POSTGRADUATE EDUCATIONAL NUMBER

Containing a Symposium on the Central Nervous System Related to Anaesthesia

British Journal of Anaesthesia

JOINT EDITORS:
E. FALKNER HILL T. CECIL GRAY
Editor of Postgraduate Educational Numbers R. P. HARBORD

Volume XXXIII No. 4 April 1961

JOHN SHERRATT & SON : *Publishers*
ALTRINCHAM ENGLAND

ALLEN & HANBURYS LTD

introduce

THE SEALEY Portable

DEFIBRILLATOR

MODEL
P.D.2

—ready for immediate use
in cardiac emergencies

DESCRIPTIVE LITERATURE AVAILABLE ON REQUEST

NOTE: This Portable Defibrillator is only one of a comprehensive range of Sealey Electrical Cardiac Resuscitation Apparatus, including internal and external defibrillators and cardiac pacemakers.

SOLE WORLD DISTRIBUTORS

ALLEN & HANBURYS LTD *(SURGICAL DIVISION)* LONDON E2

Medomin

Medomin adds to a positive hypnotic action a wide safety margin and freedom from after-effects, making it eminently suitable for patients of all ages.

Medomin presents the surety of hypnosis through the barbituric acid nucleus

Geigy

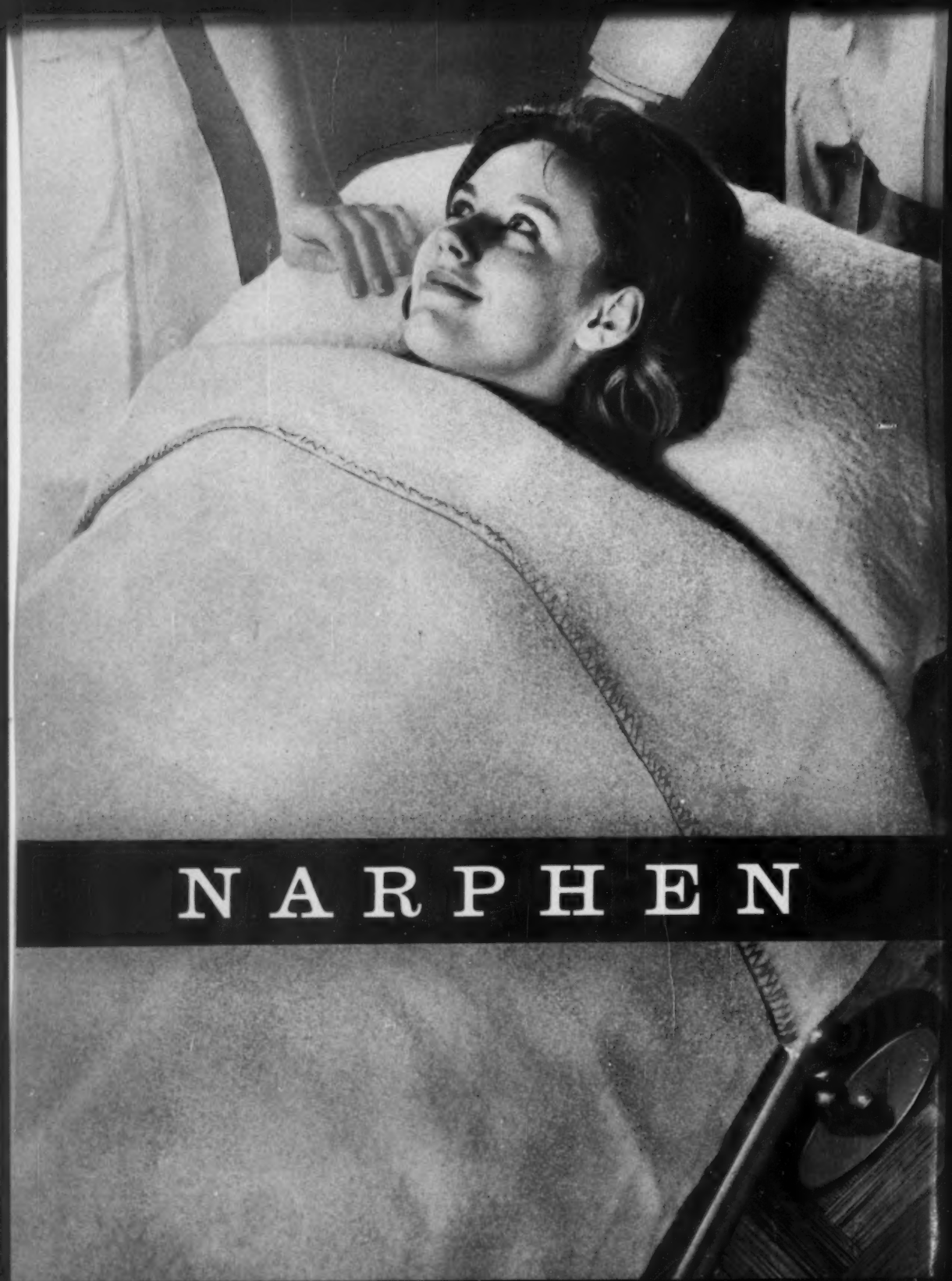
fresh awakening

Sound sleep.....

Dose: Adults 1 tablet, taken ½-1 hour before retiring. Children ¼-1 tablet, according to age.
Available in tablets of 200 mg
Heptabarbitone (Cycloheptenylethyl barbituric acid)
Containers of 10, 100, 1000

Geigy Pharmaceutical Company Ltd;
Wythenshawe, Manchester 23.

PH 183


NARPHEN

PAIN FREE BUT WIDE AWAKE...

Morphine-like analgesia
without narcosis — with NARPHEN

Narphen can supersede general anaesthetics in emergencies, minor surgery, orthopaedic procedures and obstetrics, when the full co-operation of the patient is needed. No elaborate pre-anaesthetic routine is necessary. Out-patients can be sent home and in-patients back to bed without lengthy post-operative observation.

Before, during and after general anaesthesia, Narphen controls pain efficiently and safely. It produces less respiratory depression than morphine or pethidine and does not cause hypotension. Narphen does not induce nausea or vomiting.

for deep analgesia without narcosis

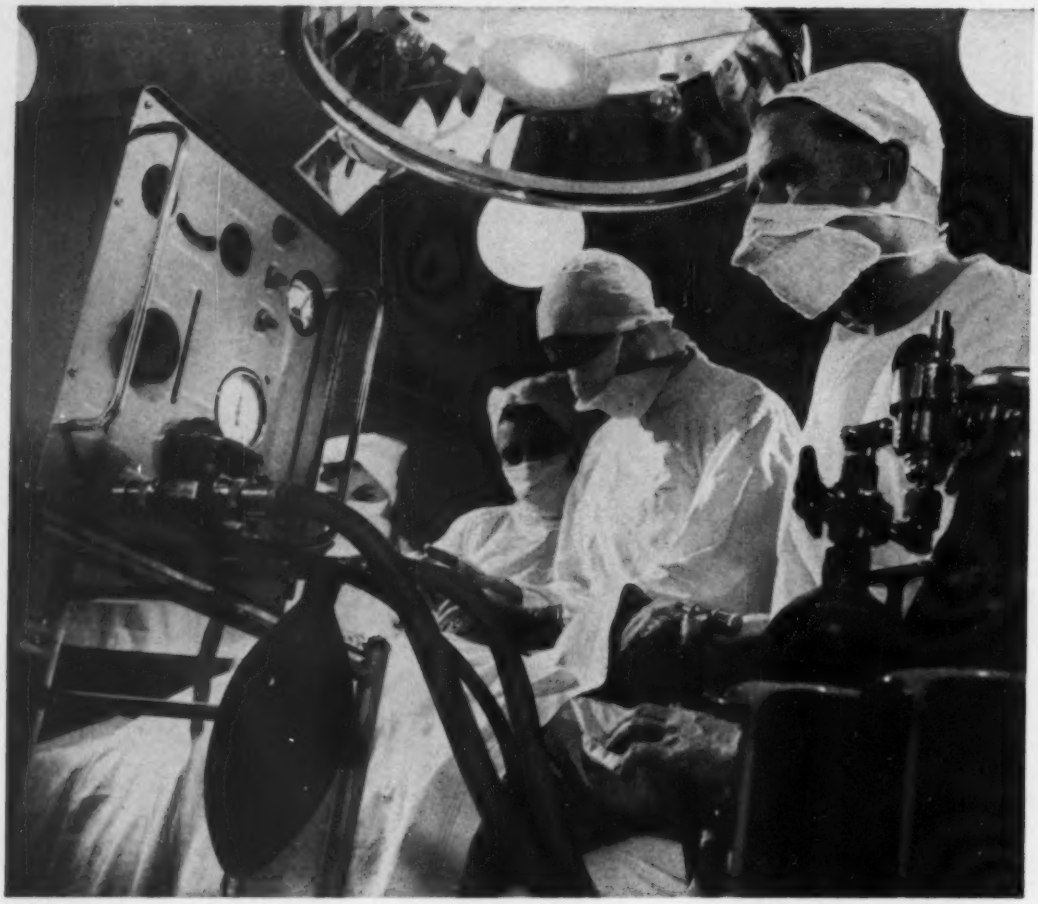
Narphen is SNP brand Phenazocine (2'-hydroxy-5,9-dimethyl-2-phenethyl-6,7-benzomorphan hydrobromide)

Available in 1.1 ml. ampoules each containing 2 mg. phenazocine hydrobromide per ml. in aqueous solution. Boxes of 10 & 100 ampoules. Basic N.H.S. cost 15/- and 120/-. Exempt from Purchase Tax.

Subject to Dangerous Drugs Regulations.

SNP

Smith & Nephew *Pharmaceuticals* Limited
WELWYN GARDEN CITY · HERTFORDSHIRE



THE BARNET VENTILATOR

WATSON

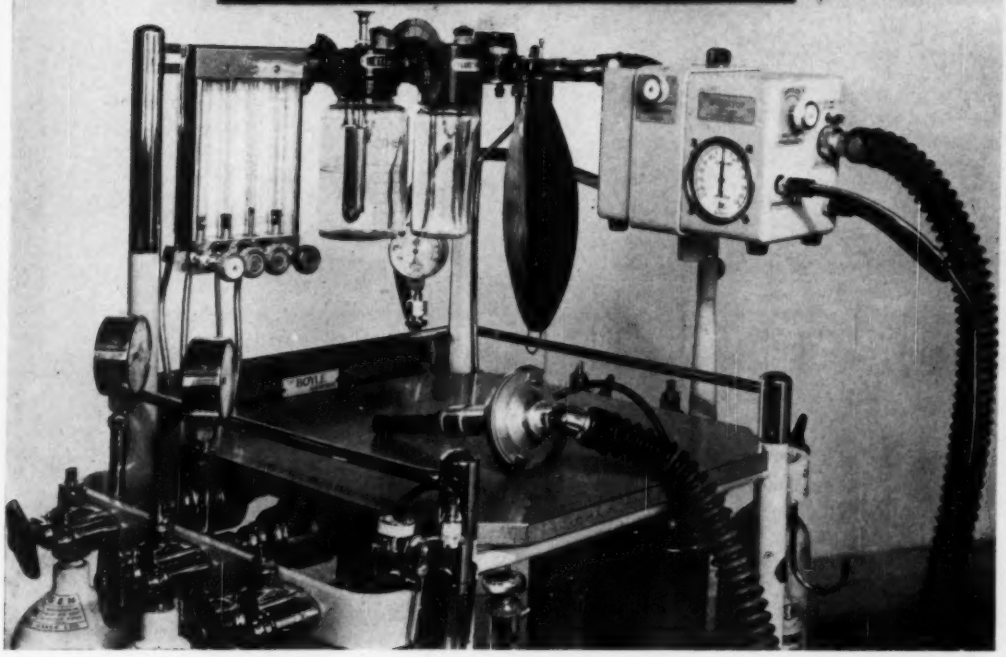
The Barnet Ventilator is a portable automatic respirator used in the operating theatre for controlled ventilation during anaesthesia.
It may be time cycled where the patient is completely relaxed, or patient cycled where spontaneous respiration is retained.
Lung ventilation is achieved by alternation of positive-atmospheric or positive-negative pressures. The Barnet Ventilator provides simple control and direct indication of inspiratory time, expiratory time, respiratory rate and tidal volume.
The equipment can also be used in the recovery room or in medical wards for long term controlled ventilation where treatment of respiratory insufficiency is necessary.
The portable weight of the Barnet Ventilator is approximately 56 lb. It employs a transistorised control circuit and operates from a built-in low voltage battery, allowing 20 hours continuous use before re-charging.

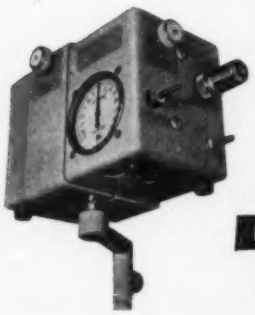
W. WATSON & SONS LIMITED · BARNET · HERTS

BRITISH OXYGEN

equipment and gases used daily in the service of medicine

CYCLATOR Type P Mark 1





The CYCLATOR Type P Mark 1 is an intermittent positive pressure lung ventilator of the pressure cycling controller type. It is intended mainly for use on the open circuit of a Boyle type anaesthetic apparatus for automatic controlled respiration. Controls are provided permitting variation of lung inflation pressure up to 35 cms. H_2O, and expiratory time between $\frac{1}{2}$ second and 30 seconds.

FOR DETAILED INFORMATION PLEASE GET IN TOUCH WITH:

THE BRITISH OXYGEN COMPANY LTD

MEDICAL DEPARTMENT, SPENCER HOUSE, 27 ST. JAMES'S PLACE, LONDON S.W.1

For modern operating and radiological techniques . . .

THE 'KIFA' UROLOGICAL TABLE

with full x-ray facilities

One of the many advantages of the 'Kifa' Urological Table is the motor-driven up and down movement, effortlessly achieved simply by depressing a foot pedal. A motorised irrigation funnel can also be supplied together with a wide range of accessories.
A fully automatic Bucky diaphragm 17″ × 14″ is built into the table top which is tiltable through 20°. The top can also slide away from the base to give access for an image intensifier or similar screening device.

SIEREX LTD

Write or telephone for further details

241 Tottenham Court Road London W.1
Telephone: LANgham 2464

SUPPLIERS OF SIEMENS AND ELEMA-SCHÖNANDER X-RAY EQUIPMENT

Send your copies of the

British Journal of Anaesthesia

for

BINDING

to

JOHN SHERRATT & SON
PARK ROAD, ALTRINCHAM

focus on anaesthesia

DEVONSHIRE STREET W1

This address is more than a familiar name to anaesthetists the world over. On display are examples of all the anaesthetic apparatus, resuscitation and oxygen therapy equipment and accessories supplied by British Oxygen — of which demonstrations can readily be given. And here is helpful information about the whole British Oxygen medical range. There is also a comprehensive anaesthetic reference library open to all visitors . . . a special display of interesting early equipment . . . facilities for the loan of equipment and lecturing aids for speakers . . . and an experimental workshop actually on the premises. Please call and see us. You are always welcome at No. 27.

THE BRITISH OXYGEN COMPANY LIMITED

MEDICAL DEPARTMENT · 27 DEVONSHIRE STREET · LONDON, W.1 · TELEPHONE: WELbeck 2202

select from the range of

Many anaesthetists have now selected those 'Pamergan' solutions which are most suited to their needs. Pre-medication, so standardized within the surgical unit, has been found to simplify prescribing and the administration by ward staff. A single, small injection is more comfortable for the patient too.

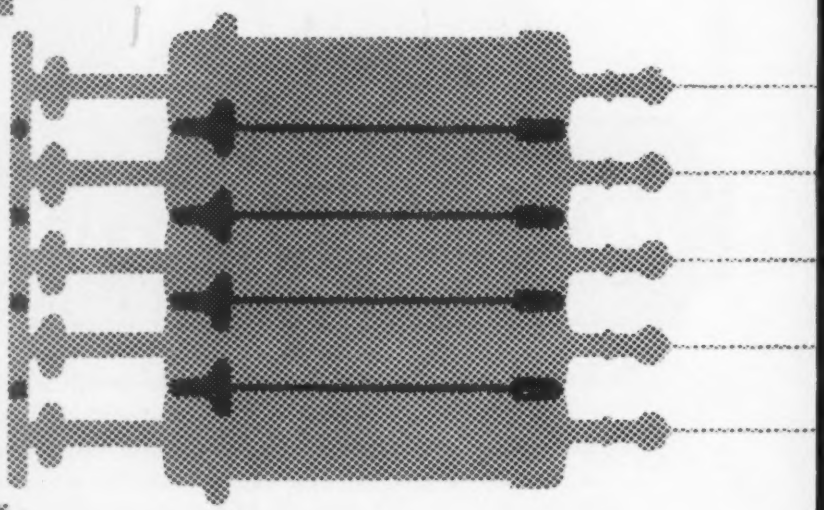
'PAMERGAN'
P.100

'PAMERGAN'
P.100/25

'PAMERGAN'
SP.50

'PAMERGAN'
SP.100

'PAMERGAN'
AP.100/25



MANUFACTURED BY
MAY & BAKER LTD
Distributors: PHARMACEUTICAL SPECIALITIES (MAY & BAKER) LTD · DAGENHAM · ESSEX

'Pamergan'

trade mark *brand*

PRE-ANAESTHETIC SOLUTIONS

'PAMERGAN' PRESENTATIONS

P.100	Pethidine Hydrochloride B.P. 100 mg. Promethazine Hydrochloride B.P. 50 mg.	*in each 2 ml. ampoule*
P.100/25	Pethidine Hydrochloride B.P. 100 mg. Promethazine Hydrochloride B.P. 25 mg.	*in each 1 ml ampoule*
SP.50	Scopolamine Hydrochloride B.P. 0·43 mg. Pethidine Hydrochloride B.P. 50 mg. Promethazine Hydrochloride B.P. 50 mg.	*in each 2 ml. ampoule*
SP.100	Scopolamine Hydrobromide B.P. 0·43 mg. Pethidine Hydrochloride B.P. 100 mg. Promethazine Hydrochloride B.P. 50 mg.	*in each 2 ml. ampoule*
AP.100/25	Atropine Sulphate B.P. 0·6 mg. Pethidine Hydrochloride B.P. 100 mg. Promethazine Hydrochloride B.P. 25 mg.	*in each 1 ml ampoule*

Detailed information is available on request

AN **M&B** BRAND MEDICAL PRODUCT

MA7977/109

CANADIAN ANÆSTHETISTS' SOCIETY JOURNAL

Editor
R. A. GORDON, C.D., B.SC., M.D., F.R.C.P.(C), F.F.A.R.C.S.

Editorial Board
ALAN B. NOBLE, M.D., F.A.C.A. — E. A. GAIN, B.A., M.D.
LOUIS LAMOUREUX, M.D. — LEON LONGTIN, M.D., F.R.C.P.(C.)

★

The Journal is issued quarterly for members of the Society and Subscribers. It contains original articles and reviews on clinical and basic science subjects related to Anæsthesia.

Annual Subscription $8.00 post paid

The Secretary
Canadian Anæsthetists Society
178 St. George Street, Toronto 5, Ontario, Canada

THE INTERNATIONAL MEDICAL ABSTRACTING SERVICE

EXCERPTA MEDICA

AMSTERDAM — LONDON — NEW YORK

offers to medical science:

For each medical specialty a MONTHLY ABSTRACTING JOURNAL containing abstracts in English from every available medical journal in the world.

Two special publications:

(1) SIDE EFFECTS OF DRUGS: an exhaustive and up-to-date review of the use of present-day drugs and their side effects, edited and compiled by L. Meyler, M.D.

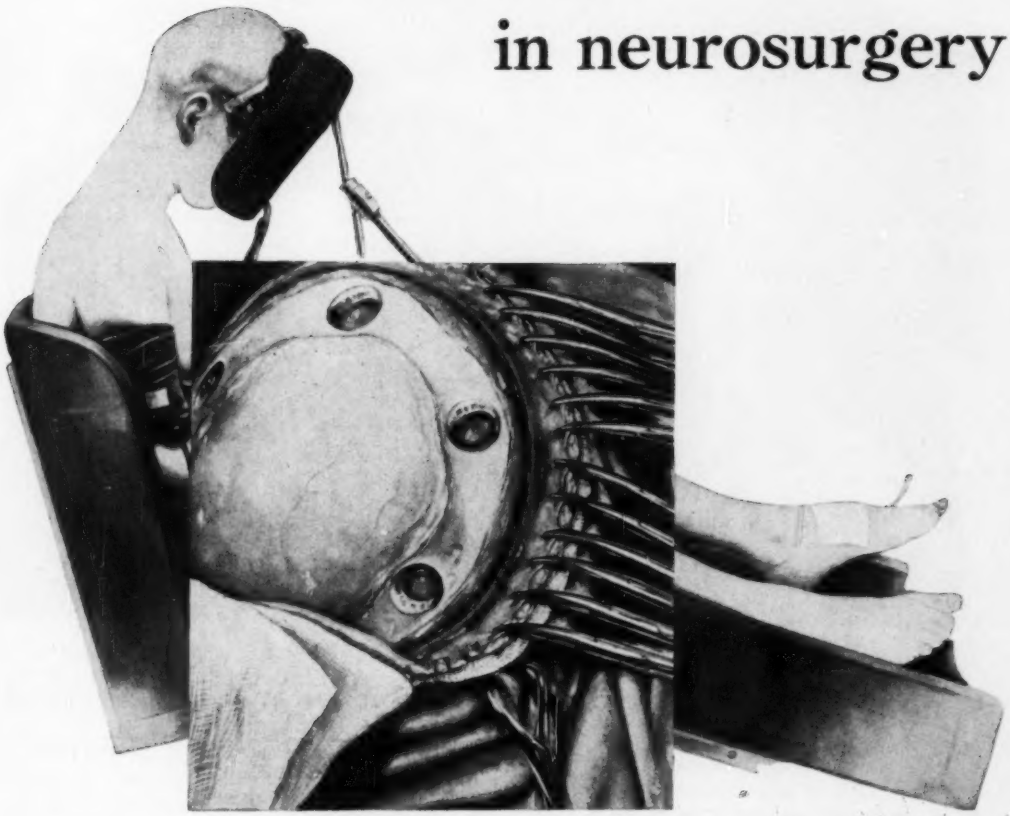
(2) PHARMACOLOGICAL AND CHEMICAL SYNONYMS: a collection of more than 8,000 references from the medical literature of the world, compiled by E. E. J. Marler, M.D., M.Sc., Ph.D.

A TRANSLATION SERVICE for the rapid translation of medical publications and manuscripts.

LONDON OFFICE: *67 New Bond Street, W.1*

Telephone Mayfair 0329

'Fluothane' in neurosurgery



'FLUOTHANE' has valuable advantages in the anaesthetic management of the neurosurgical patient. It has been used successfully for intra-cranial operations, surgery of the vertebral column and spinal cord, and the radiological investigations.

In this field attention has been drawn to the swift, smooth induction provided by 'Fluothane', the absence of respiratory tract irritation, the diminished bleeding and freedom from increases in cerebro-venous and cerebro-spinal fluid pressures. With these and other significant characteristics this non-inflammable and non-explosive anaesthetic is now making an important contribution towards improved operating conditions for the neurosurgeon and greater safety for the patient.

Fluothane - *an I.C.I discovery*

Halothane B.P. TRADE MARK

ICI IMPERIAL CHEMICAL INDUSTRIES LIMITED PHARMACEUTICALS DIVISION WILMSLOW CHESHIRE

PH110

a time for relaxation...

A short time or a long time for muscular relaxation?
B. W. & Co. provide a product for each need:

'ANECTINE' BRAND — Injection of Succinylcholine Chloride

The first choice for procedures requiring rapid muscular relaxation of brief duration.

'TUBARINE' BRAND — Preparations of Tubocurarine Chloride

The most widely-used muscle relaxant; unsurpassed for prolonged procedures, and where profound relaxation is required.

B. W. & CO. Muscle Relaxants

BURROUGHS WELLCOME & CO. (The Wellcome Foundation Ltd.) LONDON

NOTICE TO CONTRIBUTORS

This Journal is for the publication of original work in all branches of anaesthesia, including the application of basic sciences. Two issues each year deal mainly with material of educational value.

Papers. Papers are accepted on the understanding that they have not been and will not be published in whole or in part in any other journal. They are subject to editorial revision. Manuscripts should indicate the title of the paper, the name qualifications and full address of the author, and be in double-spaced typing on one side only of quarto paper with a wide margin.

Abbreviations, Weights and Measures. Abbreviations should follow the convention adopted by the *Journal of Physiology*. Weights and measures, dosages, etc., should be expressed in the metric system.

Tables. All tables should be on separate sheets and be capable of interpretation without reference to the text.

Illustrations. Photographs should be unmounted, glossy prints. Drawings, charts and graphs should be in black indian ink on white paper. All illustrations should be clearly numbered with reference to the text on the back and should be accompanied by a suitable legend. The name of the author and title of the paper should also be written on the back of the illustrations.

References. There should be a table of references at the conclusion of the paper. These references should be arranged according to the Harvard system and in alphabetical order. Abbreviations in the references should be according to the World List of Scientific Publications.

In the Harvard system, in the text the year of publication must follow the author's name, more than one paper in any one year being indicated by a small letter (a, b, c) after the date. In the references, the order should be: author's name, followed by initials; year of publication in parentheses; title of paper to which reference is made; title of publication underlined with a singe line (to indicate italics) and abbreviated in accordance with the World List of Scientific Periodicals; volume number in arabic numerals, underlined with a wavy line (to indicate bold face); the number of the first page in arabic numerals; thus: Howell, T. H., Harth, J. A. P., and Dietrich, M. (1954). The use of chlorpromazine in geriatrics. *Practitioner*, **173**, 172.

In the case of books, the reference should be as follows: name of author and initials; year of publication in parentheses; title of book; number of edition; page number; town of origin, publisher; e.g., Hewer, C. L. (1948). *Recent Advances in Anaesthesia and Analgesia*, 6th ed., p. 120. London: Churchill.

The *British Journal of Anaesthesia* should be referred to in the references as *Brit. J. Anaesth.*

Proofs. Proofs will be sent to all contributors. These should be corrected and returned to the Joint Editors within forty-eight hours.

Reprints. Twenty-five reprints of articles will be dispatched to the authors after publication. Further reprints can be supplied if application is made when the proofs are returned.

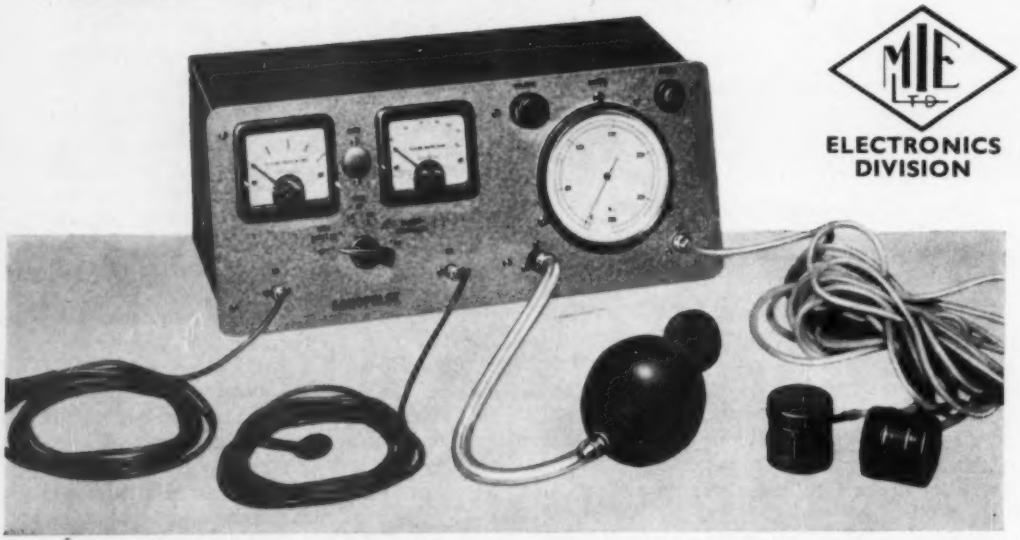
Copyright. Papers which have been published become the property of the Journal and permission to republish must be obtained from the Editors.

The

SONOPULSE

TRANSISTORISED

PULSE · SOUND · VISION · RATE and
BLOOD PRESSURE RECORDER *by*



MIE LTD
ELECTRONICS DIVISION

MEDICAL & INDUSTRIAL EQUIPMENT LTD.

SPECIALISTS IN ANAESTHETIC APPARATUS & SURGICAL INSTRUMENTS

10 & 12 NEW CAVENDISH STREET, LONDON W.1
Telephone : WELbeck 1851 and 1504 *Telegrams : Narcosis, Wesdo, London*

MANCHESTER, 152-154 Oxford Road
Phone : Ardwick 5906

TORONTO, CANADA, 132, St. Patrick Street
Phone : WALNUT 3-3845

All enquiries concerning

ADVERTISING SPACE IN THIS JOURNAL

should be addressed to the Advertising Agent

Mrs. K. BLOMFIELD
3 CROSWELL, GOOSE LANE
MAYFORD
WOKING, SURREY

Telephone WOKING 6171

EDITORIAL EXECUTIVE COMMITTEE

General Editors

*E. FALKNER HILL, *Late Senior Anaesthetist, Manchester Royal Infirmary*

*T. CECIL GRAY, *Professor of Anaesthesia, University of Liverpool*

Editor of Postgraduate Educational Numbers

*R. P. HARBORD, *Reader in Anaesthetics, University of Leeds*

Consultant Editors

*M. H. ARMSTRONG DAVISON, *Consultant Anaesthetist, The United Newcastle upon Tyne Teaching Hospitals*

*J. W. DUNDEE, *Senior Lecturer in Anaesthetics, Queen's University of Belfast, Northern Ireland*

*W. W. MUSHIN, *Professor of Anaesthetics, Welsh National School of Medicine, Wales*

*J. F. NUNN, *Research Fellow, Royal College of Surgeons of England; Lecturer, University of London*

*H. H. PINKERTON, *Joint Lecturer in Anaesthetics, University of Glasgow, Scotland*

*R. F. WOOLMER, *Professor of Anaesthetics, Department of Anaesthesia, Royal College of Surgeons of England, London*

Assistant Editors

A. R. HUNTER, *Consultant Anaesthetist, Manchester Royal Infirmary*

J. E. RIDING, *Demonstrator in the Department of Anaesthesia, University of Liverpool*

Honorary Treasurer

*R. J. MINNITT, *Late Senior Honorary Anaesthetist, Royal Liverpool United Hospitals*

*In addition to those individuals on the EDITORIAL EXECUTIVE COMMITTEE whose names are marked with an asterisk, the following are members of the BOARD OF MANAGEMENT AND PROPRIETORS:

R. C. LAWRENCE, *Consultant Anaesthetist, United Leeds Hospitals*
T. J. C. MACDONALD, *Consultant Anaesthetist, Aberdeen Royal Infirmary*
A. G. MILLER, *Consultant Anaesthetist, Western Infirmary, Glasgow*
R. E. PLEASANCE, *Lecturer in Anaesthetics, University of Sheffield*
H. Q. O. WHEELER, *Consultant Anaesthetist, Department of Neurological Surgery, General Hospital, Sunderland*
W. D. WYLIE, *Consultant Anaesthetist, St. Thomas's Hospital, London*

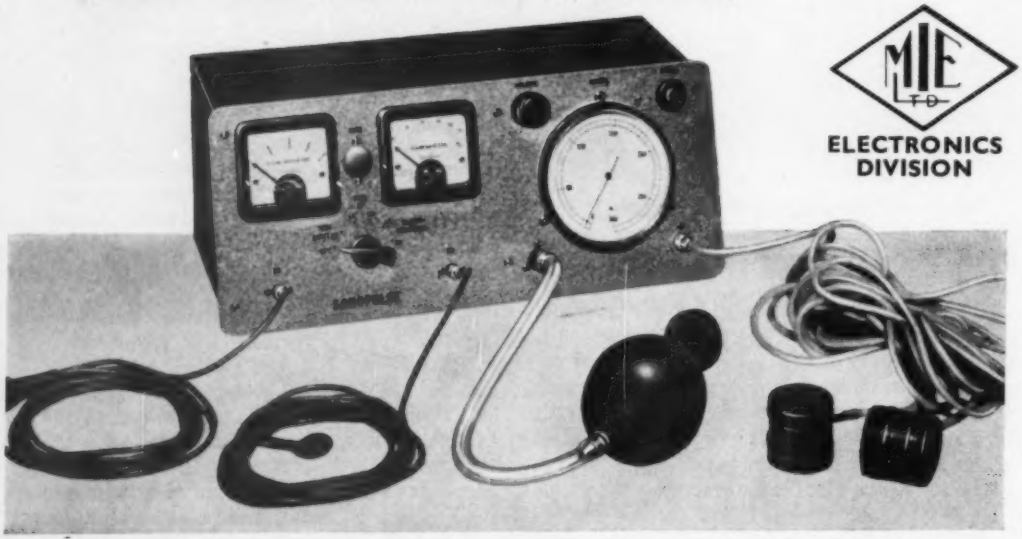
Papers for publication and all editorial communications should be addressed to either of the Editors at 48–50 Bedford Street North, Liverpool, 7. Business communications should be addressed to the publishers: JOHN SHERRATT AND SON, Park Road, Altrincham, Cheshire. Published monthly. Annual subscriptions (post free): Inland £3 15s.; Overseas £4 4s.; United States and South Americas $12.00. © John Sherratt and Son, 1961.

The

SONOPULSE

TRANSISTORISED

PULSE · SOUND · VISION · RATE and
BLOOD PRESSURE RECORDER *by*



MIE LTD
ELECTRONICS DIVISION

MEDICAL & INDUSTRIAL EQUIPMENT LTD.

SPECIALISTS IN ANAESTHETIC APPARATUS & SURGICAL INSTRUMENTS

10 & 12 NEW CAVENDISH STREET, LONDON W.1

Telephone : WELbeck 1851 and 1504 *Telegrams : Narcosis, Wesdo, London*

MANCHESTER, 152-154 Oxford Road
Phone : Ardwick 5906

TORONTO, CANADA, 132, St. Patrick Street
Phone : WALNUT 3-3845

All enquiries concerning

ADVERTISING SPACE IN THIS JOURNAL

should be addressed to the Advertising Agent

Mrs. K. BLOMFIELD
3 CROSWELL, GOOSE LANE
MAYFORD
WOKING, SURREY

Telephone WOKING 6171

EDITORIAL EXECUTIVE COMMITTEE

General Editors

*E. FALKNER HILL, *Late Senior Anaesthetist, Manchester Royal Infirmary*

*T. CECIL GRAY, *Professor of Anaesthesia, University of Liverpool*

Editor of Postgraduate Educational Numbers

*R. P. HARBORD, *Reader in Anaesthetics, University of Leeds*

Consultant Editors

*M. H. ARMSTRONG DAVISON, *Consultant Anaesthetist, The United Newcastle upon Tyne Teaching Hospitals*

*J. W. DUNDEE, *Senior Lecturer in Anaesthetics, Queen's University of Belfast, Northern Ireland*

*W. W. MUSHIN, *Professor of Anaesthetics, Welsh National School of Medicine, Wales*

*J. F. NUNN, *Research Fellow, Royal College of Surgeons of England; Lecturer, University of London*

*H. H. PINKERTON, *Joint Lecturer in Anaesthetics, University of Glasgow, Scotland*

*R. F. WOOLMER, *Professor of Anaesthetics, Department of Anaesthesia, Royal College of Surgeons of England, London*

Assistant Editors

A. R. HUNTER, *Consultant Anaesthetist, Manchester Royal Infirmary*

J. E. RIDING, *Demonstrator in the Department of Anaesthesia, University of Liverpool*

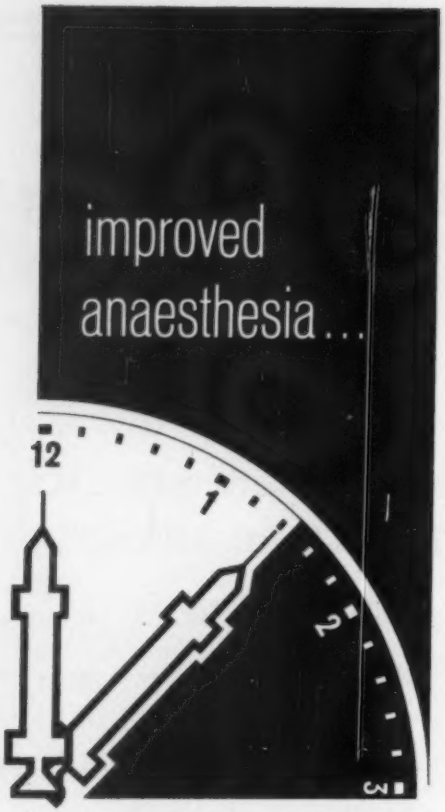
Honorary Treasurer

*R. J. MINNITT, *Late Senior Honorary Anaesthetist, Royal Liverpool United Hospitals*

*In addition to those individuals on the EDITORIAL EXECUTIVE COMMITTEE whose names are marked with an asterisk, the following are members of the BOARD OF MANAGEMENT AND PROPRIETORS:

R. C. LAWRENCE, *Consultant Anaesthetist, United Leeds Hospitals*
T. J. C. MACDONALD, *Consultant Anaesthetist, Aberdeen Royal Infirmary*
A. G. MILLER, *Consultant Anaesthetist, Western Infirmary, Glasgow*
R. E. PLEASANCE, *Lecturer in Anaesthetics, University of Sheffield*
H. Q. O. WHEELER, *Consultant Anaesthetist, Department of Neurological Surgery, General Hospital, Sunderland*
W. D. WYLIE, *Consultant Anaesthetist, St. Thomas's Hospital, London*

Papers for publication and all editorial communications should be addressed to either of the Editors at 48–50 Bedford Street North, Liverpool, 7. Business communications should be addressed to the publishers: JOHN SHERRATT AND SON, Park Road, Altrincham, Cheshire. Published monthly. Annual subscriptions (post free): Inland £3 15s.; Overseas £4 4s.; United States and South Americas $12.00. © John Sherratt and Son, 1961.



..for brief operative procedures

Here is a new, more potent intravenous barbiturate, 'Brietal Sodium', which ensures smooth induction of anaesthesia and rapid, clear-headed recovery.
'Brietal Sodium' is of particular value in:

electro-shock · dental surgery
obstetrics · orthopaedics
reduction of fractures · general surgery
gynaecological examination

'BRIETAL SODIUM'

Trade Mark — Brand

METHOHEXITONE SODIUM

The average dose is 50-100 mg. in a 1% solution. 'Brietal Sodium' is supplied in ampoules each containing 0·5 Gm.

Lilly

ELI LILLY AND COMPANY LIMITED · BASINGSTOKE · ENGLAND

"*I would have everie man write what he knowes and no more.*"—MONTAIGNE

BRITISH JOURNAL OF ANAESTHESIA

VOL. XXXIII, No. 4 APRIL 1961

EDITORIAL

ON SYMPOSIA AND LEARNING

For out of old fieldes, as men saithe
Cometh all the new corn, fro yere to yere,
And out of old bookes, in good faithe
Cometh all this new science that men lere.
CHAUCER

A MAN can be well versed in the writings of others and yet know little of his subject. Knowledge of what has been written may not be the same as understanding what happens, and this applies with special force to practical disciplines. More knowledge accumulates each year and the increase is *progressive*. To know where to find reviews of reviews is all very helpful now, but what of the year 2061? Perhaps when so much has accumulated no one will be able to retain enough within his cranium to understand! At present man has not sifted his ideas sufficiently well to grasp the significance of his own consciousness.

Although we are aware of what it feels like to be conscious, its precise definition is elusive despite many comparatively new works on the subject. An Anglo-American symposium held in 1957 in London on the history and philosophy of knowledge of "The Brain and its Functions" goes back well beyond Chaucer into the lore of classical antiquity. In 1953 the symposium on "Brain Mechanisms and Consciousness" was held in a chalet on the Laurentian mountains. From these heights the participants devoted a section to "The Action of Anaesthetics on the Nervous System" and their thoughts turned towards the functional significance of the brain stem reticular system. Before the Laurentian symposium there had been several reviews dealing with the way in which anaesthetics affect the nervous system (Winterstein, 1926; Henderson, 1930; Gerard, 1947; Toman and Davis, 1949; Butler, 1950; Mécanisme de Narcose, Paris, 1951), but these did not consider fully that the specific afferent systems in the brain are not the only route to the cortex; each failed to emphasize the part played by the ascending system of the reticular formation of the brain stem.

In 1957 the old and the new were again considered in a symposium in London on "Neurological Basis of Behaviour" in the light of recent advances in knowledge. At the end of this Penfield stated: "It is difficult to bring work like that of Eccles, Magoun, Gastaut, Malcolm (to mention only a few) together momentarily, but it will come in time."

The prodigious efforts of research workers from all over the world deal in large measure with animal work and with ether and barbiturates; only a few have come from practising anaesthetists who render patients unconscious every day with anaesthetic agents and techniques, such as, for example, hyperventilation, having significant physiological influences on the nervous system. These open new and exciting fields of knowledge which clinicians are now exploring. It is doubtful if those engaged primarily on unravelling the secrets of anaesthesia are knowledgeable about current agents and procedures.

ACKNOWLEDGMENT

The editors are grateful to Dr. John Clutton-Brock for much valuable advice in connection with the preparation of the symposium in this issue of the Journal.

REFERENCES

Butler, T. C. (1950). Theories of general anaesthesia. *J. Pharmacol.*, **98**, 121.
Gerard, R. W. (1947). Anesthetics and cell metabolism. *Anesthesiology*, **8**, 453.
Henderson, V. E. (1930). Present status of theories of narcosis. *Physiol. Rev.*, **10**, 171.
Mécanisme de la Narcose. Paris Centre National de la Recherche Scientifique), 1951.
Toman, J. E. P., and Davis, J. P. (1949). Effects of drugs upon electrical activity of brain. *J. Pharmacol.*, **97**, 425.
Winterstein, H. (1926). *Die Narkose*, 2nd ed. Berlin: Springer.

SYMPOSIA

Neurological Basis of Behaviour (1957). London: J. & A. Churchill, Ltd.
The Brain and its Functions (1957). Oxford: Blackwell Scientific Publications.
Brain Mechanisms and Unconsciousness (1953). Oxford: Blackwell Scientific Publications.

Brit. J. Anaesth. (1961), 33, 174

THE RETICULAR FORMATION AND ASCENDING RETICULAR SYSTEM: ANATOMICAL CONSIDERATIONS

BY

DAVID BOWSHER
Department of Anatomy, University of Liverpool, England

IN the past decade neurological scientists have laid great emphasis on the structure, and particularly the function, of the reticular formation. A great deal of information has been collected on the subject, but most of it still lies scattered among a large number of journals and published symposia, the standard textbooks still having very little to offer on this important topic.

Although recent interest in the reticular formation and the related diffuse thalamo-cortical projection system dates from the important papers of Magoun and McKinley (1942) and Moruzzi and Magoun (1949), its importance and possible functions had been recognized much earlier in a publication by Kohnstamm and Quensel (1908).

While it would be unnecessarily tedious to review the whole literature on the subject in an article of this nature, the essential structure and connections of the reticular formation, so far as they are at present known, may be summarized. The sections which follow will be devoted to the morphology, connections and anatomico-functional correlates of the reticular formation and the diffuse thalamo-cortical projection, with particular emphasis on that part which is known as the ascending reticular system.

I. *Morphology* (fig. 1).

The reticular formation as anatomically defined consists of neurones more or less scattered among the criss-cross fibre meshwork (hence the name) of the medulla, pons and midbrain. In the brain stem these may further be defined as those tegmental cells which are not (i) cranial nerve nuclei, or (ii) sensory or cerebellar relay nuclei (e.g. gracile, cuneate, external cuneate, lateral reticular—better called by its old name, the nucleus of the lateral funiculus, in order to avoid confusion—olivary, pontine and red). While this definition sounds comparatively simple in anatomical terms, it should at once be pointed out that the boundary between some of the reticular and nonreticular cell groups (and particularly the sensory cranial nerve nuclei) are not at all clearly delimited, so that it would be impossible to say in these cases, on histological inspection, exactly which cells are reticular and which are not.

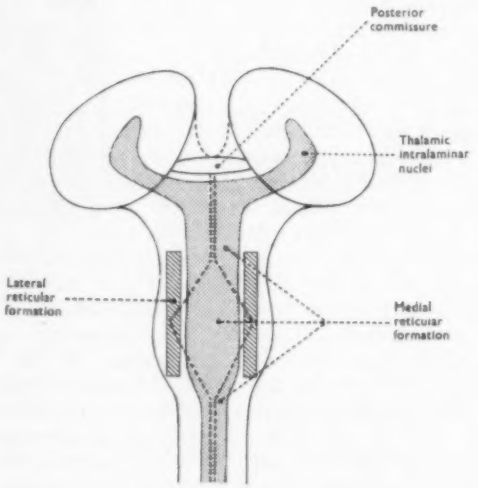


FIG. 1

Diagrammatic representation of the medial and lateral parts of the reticular formation. Note the continuity of the former with the intralaminar nuclei of the thalamus and the spinal reticular formation.

Although this may be an adequate description of the reticular formation of the brain stem in strictly anatomical terms, it is important to realize that the system, in functional terms, has a much greater extension in both rostral and caudal directions than this purely histological definition

would imply. We are accustomed to thinking of certain cell types as lying in columns in the long axis of the central nervous system, e.g., the somatic motor column, which includes the anterior horn cells of the spinal cord, and the motor nuclei of the IIIrd, IVth, VIth and XIIth cranial nerves. So it is with the reticular system. In the spinal cord there are many cells, mostly grouped round the central canal, which do not belong to either the motor or sensory systems of the anterior or posterior horns of the grey matter. As these cells are traced up into the medulla, they become continuous with the more scattered cells of the medial part of the reticular formation proper, and it is important to realize that functionally these cells are part and parcel of the same system. Similarly, in a rostral direction, the cells of the brain stem reticular formation are structurally and functionally continuous with the cells of the intralaminar group of thalamic nuclei, and probably with certain ill-defined cell groups in the neighbourhood of the medial geniculate body (fig. 1).

Many attempts have been made to segregate the cells of the brain stem reticular formation into definitive "nuclei", but the very nature of the brain stem structure makes this an exceedingly difficult task, and few authors are in agreement on the boundaries of these so-called nuclei. However, the standard work on the morphology of these cells is the atlas of Olszewski and Baxter (1954), to which the student in search of more precise anatomical information is referred.

The cell types encountered in the reticular formation vary from very large (e.g. the nucleus giganto-cellularis of the rostral medulla) to small, and no satisfactory classification can be made on this basis. The most practical approach is to divide the reticular formation into medial and lateral portions. The medial reticular formation includes all the reticular cells of the spinal cord and intralaminar thalamic nuclei, and the more centrally placed (medial two-thirds) reticular cells of the brain stem. The lateral part of the reticular formation, on the other hand, is only encountered in the lower brain stem, and may be roughly defined as that portion in which the descending and principal sensory nuclei of the trigeminal nerve are embedded.

Although a reticular formation is found in the most primitive brains, it should not be assumed that its importance diminishes as the phylogenetic scale is ascended. Indeed, Hines (1955) has stated that in man the reticular formation is relatively and absolutely larger than in lower animals; the same is true of the intralaminar nuclei of the thalamus, and particularly the centre median (Simma, 1957).

II. *The ascending reticular system and its afferent connections.*

Most cells of the lateral part of the brain stem reticular formation send their axons into the adjacent medial reticular formation. None of them give off long descending axons, thus there is no lateral reticulo-spinal pathway. Of the cells in the medial part of the brain stem reticular formation, some send their axons rostrally and some caudally; yet others have axons which bifurcate into ascending and descending branches.

Those cells which send their axons in a rostral direction are known collectively as the ascending reticular system. It is important not to confuse this system with the reticular formation as a whole, of which it is only a part. But it is the part that has been most extensively studied, and with which the present article is chiefly concerned. The reticular arousal system of current physiology is contained within the ascending reticular system of anatomical nomenclature, but it is not known whether the arousal system is co-extensive with the ascending reticular system or not.

Impulses passing through the ascending reticular system are finally relayed through the intralaminar nuclei of the thalamus and reach the cortex via the diffuse thalamo-cortical projection. It is thus of some importance to know which parts of the reticular formation belong to the ascending system, and whence they receive their afferents. Most of the recent experimental work has been carried out on the cat and monkey, but such evidence as there is from human studies reveals that the organization is essentially similar.

1. *Spino-reticular afferents.* A large number of fibres from the antero-lateral quadrant of the cord terminate in the brain stem reticular formation. The existence of such fibres in man had been observed as early as 1903 by Collier and Buzzard. Many authors have noted that the so-called "spino-thalamic tract" diminishes rapidly in size as it ascends through the brain stem, and

Glees (1953) has estimated that it contains only some 1,500 fibres at mesencephalic level. Although many ascending fibres from the antero-lateral quadrant of the cord terminate in the cerebellum and its relay nuclei, and in certain of the sensory cranial nerve nuclei, most of them appear to end around cells of the reticular formation. Quantitative evidence suggests that these spino-reticular fibres are not, as has been suggested by some physiologists, collaterals of long ascending systems, but independent axons originating in the cord and terminating exclusively in the reticular formation (see Section VI).

In this connection it is interesting to note that no fibres from the dorsal columns of the cord terminate in the reticular formation in the rat (Torvik, 1956) or cat (Matzke, 1949). Bowsher (1958) has shown that there are no connections between the medial lemniscus and the brain stem reticular formation in the macaque. However, Glees and Soler (1951) demonstrated that only some 25 per cent of the fibres in the dorsal columns reach the gracile and cuneate nuclei of the medulla in the cat. It is possible that these other dorsal column fibres synapse with cells of the spinal reticular formation, which may then secondarily project up to the brain stem reticular formation through the antero-lateral quadrant of the cord.

The most careful work on the termination of spino-reticular fibres has been performed in the cat by Rossi and Brodal (1957). They show that, although these fibres end throughout the ponto-medullary reticular formation, they are particularly concentrated in two areas of the medial reticular formation (fig. 2). In man, spino-reticular

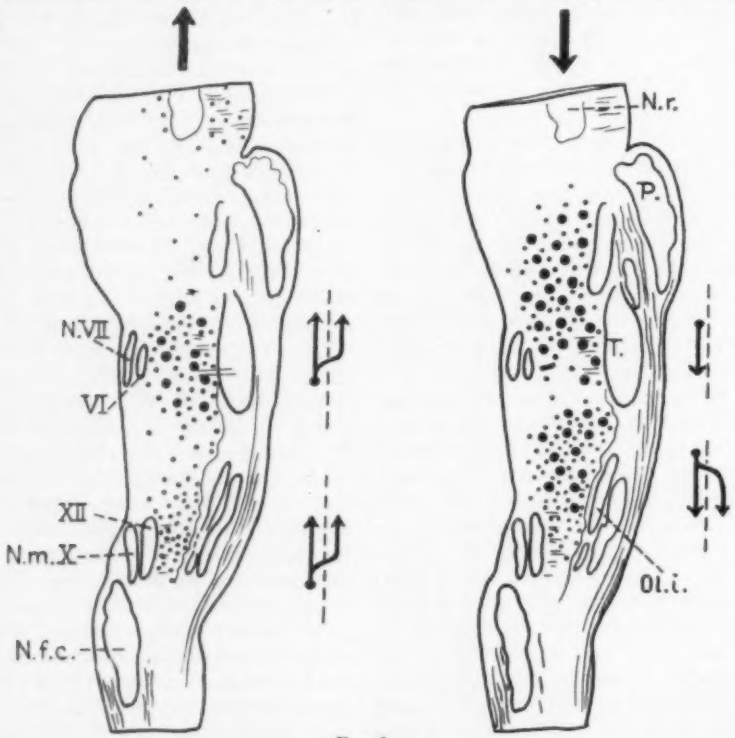


FIG. 2

Ascending and descending reticular neurones of the cat's brain stem. (Reproduced by permission, from Brodal, *The Reticular Formation of the Brain Stem*, 1957. Edinburgh: Oliver and Boyd.)

endings have also been observed at more rostral levels in the mesencephalic reticular formation (Petrén, 1910; Walker, 1940; Bowsher, 1957).

Spino-reticular afferents, about which more is known than other reticular afferents, appear to have the following properties: (*a*) they are probably stem fibres and not collaterals of long ascending systems—certainly the medial lemniscus does not contribute to the reticular formation, and all such fibres travel in the antero-lateral columns of the cord; (*b*) although some endings are found throughout the reticular formation, terminals appear to be concentrated in particular areas, indicating some degree of rostro-caudal and medio-lateral organization in the anatomy of the reticular formation.

2. *Trigeminal afferents.* These fibres are functionally of the same nature as the dorsal root fibres of the spinal cord, and thus one would expect them to be distributed to the reticular formation in much the same way as spinal afferents. Unfortunately there is as yet little precise anatomical evidence about these connections, although there are many physiological observations which prove their existence. Torvik (1956), in the rat, reports that primary afferent fibres (or their collaterals) of the Vth, VIIth, IXth and Xth nerves terminate in the dorso-lateral part of the reticular formation in the rat. Walker (1939) established that there are connections between the spinal (descending) nucleus of the trigeminal nerve and the lateral reticular formation in the macaque. Nauta and Kuypers (1959) further report that fibres from the descending trigeminal nucleus reach the medial reticular formation, and are distributed in much the same manner as spino-reticular afferents, whereas the principal sensory nucleus of the Vth nerve does not appear to have connections with the reticular formation (cf. the dorsal column nuclei, which are the spinal homologue). The findings with regard to the descending nucleus have recently been confirmed in the author's laboratory. Since it is known that most cells of the lateral reticular formation send their axons into the medial reticular formation (Scheibel, 1955), it would appear that a large number of impulses from the sensory cranial nerves and their nuclei must eventually be brought to bear on the ascending reticular system.

Hawkes (1960) has demonstrated extensive connections between the nucleus of the solitary tract and the reticular formation.

Fibres from the lateral vestibular nucleus have been shown to project into the medial reticular formation (Cajal, 1909; Lorente de Nò, 1933) and Ferraro, Pacella and Barrera (1940) have suggested that other vestibular nuclei may also project into the reticular formation in the macaque.

3. *Auditory afferents.* It has long been known that auditory stimuli are highly effective in desynchronizing the e.e.g. to produce the pattern of the arousal reaction. Perhaps the most convincing experiment is that reported by Magoun (1952), who showed that cats in which the lateral lemniscus (i.e. the direct auditory pathway) has been cut could still be aroused by auditory stimuli. Again, precise anatomical information about the auditory input to the reticular formation is lacking. Stotler (1953) has demonstrated some connections of this nature from the superior olive.

III. *Ascending reticular fibres.*

Most, if not all, cells in the medial brain stem reticular formation have long axons which ascend or descend in the central core of the grey matter. This section is concerned with those reticular neurons which give off ascending fibres. Most of these fibres travel up to the intralaminar group of thalamic nuclei (Singer and Yakovlev, 1954). If we consider afferents to the intralaminar nuclei from the level of the caudal brain stem, these fall into three main groups: (i) Long direct fibres passing from the spinal cord to the intralaminar nuclei. These fibres, few in number, are currently known as the "palaeo-spino-thalamic pathway", and have been demonstrated in the cat by Getz (1952), in the macaque by Mehler, Feferman and Nauta (1956) and in man by Bowsher (1957). (ii) Direct fibres from the caudal brain stem reticular formation to the intralaminar nuclei, demonstrated anatomically by Nauta and Kuypers (1958) in the cat. (iii) Pathways from the caudal brain stem reticular formation to cell stations in the rostral brain stem reticular formation (also demonstrated by Nauta and Kuypers) which in their turn project on to the intralaminar nuclei, as shown by numerous electrophysiological experiments.

Brodal and Rossi (1955) have shown that the zones of the medial brain stem reticular formation in the cat which give rise to ascending axons are

the same as those which receive spino-reticular afferents. Thus it may be seen that spinal input to the intralaminar thalamic nuclei may be direct from the cord, disynaptic (relaying once in the brain stem reticular formation) or polysynaptic (travelling through two or more reticular relays). Thus a single stimulus applied to the skin of the trunk or limbs will arrive at the thalamic intralaminar nuclei as a bombardment of impulses spread out in time due to synaptic delay in the later phases.

IV. *The diffuse thalamo-cortical projection.*

The ability of the intralaminar nuclei to activate the whole cortex and to desynchronize the e.e.g. was discovered by Morison and Dempsey in 1942. The most important of these rather ill-defined nuclei is the centre median, which Morison, Finley and Lothrop (1943) refer to as the "master oscillator" of the diffuse projection system.

The anatomical manner by which these nuclei project to the cortex is still far from certain. Total cortical ablation does not produce retrograde degeneration in any of them, so that there is presumably no direct connection between them and the cortex. Two possible pathways have some basis in known anatomy:

(i) There is probably a connection between the intralaminar nuclei and the thalamic reticular nucleus (Jasper and Ajmone-Marsan, 1950; Papez, 1956). This latter, lying between the external medullary lamina and the internal capsule, appears to project in a diffuse manner to the whole cortex (Rose, 1952; Macchi and de Risio, 1954). In addition to this, the intralaminar nuclei also project to the thalamic nucleus ventralis anterior (Nauta and Whitlock, 1954; Macchi, Angeleri and Carreras, 1956). This nucleus in its turn projects diffusely to the frontal cortex (Angeleri and Carreras, 1956). Thus the frontal cortex receives a "double dose" of diffuse projections, one from the thalamic reticular nucleus and the other from the nucleus ventralis anterior thalami. That the diffuse projection to the frontal association cortex is quantitatively greater than that to other cortical areas in the monkey was demonstrated by Starzl and Whitlock (1952). Hanbery, Ajmone-Marsan and Dilworth (1954) have shown that destruction of the reticular or anterior ventral nuclei of the thalamus abolishes the recruiting response in the cortex.

(ii) Nauta and Whitlock (1954) and Powell and Cowan (1956) have shown that the intralaminar nuclei of the thalamus project directly to the corpus striatum. While the cortical projections of the corpus striatum are still uncertain, Mettler, Grundfest and Hovde (1952) have suggested that it projects to the frontal cortex; Purpura, Housepian and Grundfest (1958) have recently confirmed a connection between the head of the caudate nucleus and the frontal cortex. Hewitt (1959), on embryological grounds, considers that the development of a part of the caudate nucleus is related to the development of the cortex. It is therefore possible, though as yet not satisfactorily proven, that diffuse thalamo-cortical impulses may be mediated via the corpus striatum.

V. *The descending reticular system and its connections.*

Several regions of the medial reticular formation have been shown to give off long descending axons. As early as 1899, Kohnstamm demonstrated the presence of a reticulo-spinal projection. Torvik and Brodal (1957) have shown in the cat that there are two zones in the lower brain stem, lying just rostral to the regions giving off ascending axons in which the majority of long descending axons originate. Descending reticular neurones in the midbrain tegmentum project to those regions of the pontomedullary reticular formation which give off descending axons, and some of them may project down directly into the cord. As already mentioned, the lateral reticular formation of the pons and medulla projects medially, and so influences descending reticular neurones in the medial reticular formation. It is important to realize that there is no direct lateral reticulo-spinal pathway.

Afferent projections to the descending reticular formation come from two main sources, the cerebellum and the forebrain, but mention should also be made of tecto-reticular fibres, arising in the corpora quadrigemina of the midbrain (Pearce and Glees, 1956).

Cerebellar afferents to the reticular formation appear to arise mainly from the fastigial nuclei, although some contributions come from the more laterally placed nuclei, of which the chief is the dentate. Fibres from the fastigial nucleus reach the brain stem chiefly, if not entirely, through the inferior cerebellar peduncle, travelling ipsilaterally

as direct fastigio-bulbar fibres, or contralaterally as the uncinate fasciculus. Reticulopetal fibres in these bundles appear to terminate mostly in the lateral part of the pontomedullary reticular formation in the cat (Gray, 1926; Jansen, 1954). Fibres leaving the cerebellum in the superior peduncle (brachium conjunctivum) and arising mainly from the lateral nuclei, are distributed to the medial reticular formation of the pons and medulla (Allen, 1924); an observation more recently confirmed in the macaque by Carrea and Mettler (1954).

Reticular afferents from the forebrain arise from both the cortex and basal ganglia. Kuypers (1958) found that in the cat the premotor area in particular projects to the medial reticular formation of the medulla, while Rossi and Brodal (1956) found terminations of cortical fibres in both pontine and medullary reticular formation in the same animal. Johnson and Clemente (1959) report the presence of fibres passing from the globus pallidus to the tegmental reticular nucleus of the midbrain.

In general, physiological work has shown the medial part of the medullary reticular formation to exert an inhibitory influence on spinal motor activity, while stimulation of the lateral part of the reticular formation has a facilitatory effect on motor activity. As the neurones of the lateral reticular formation project only to the medial reticular formation, and there is no direct lateral reticulo-spinal pathway, it must be assumed that lateral reticular neurones inhibit the (inhibitory) neurones of the medial reticular formation, so producing facilitation. In the case of fastigial efferents to the lateral reticular formation, some of these cells are actively inhibited by fastigial stimulation, but others are facilitated, so that at present it is not possible to account for the general inhibitory effect of fastigial stimulation on spinal motor activity.

Brodal (1957) has pointed out that the caudally-projecting zones of the medial reticular formation in the cat lie just rostral to the regions giving off ascending fibres. Ascending axons therefore pass through the dendritic fields of caudally-projecting neurones, and vice versa. It is therefore highly probable that ascending and descending reticular impulses may interact on each other at a lower brain stem level (fig. 2).

VI. *Functional correlates of the ascending reticular system.*

It has been assumed until very recently that reticular afferents are collaterals of the long ascending (lemniscal) systems. As regards the auditory pathway (lateral lemniscus), no anatomical evidence is as yet to hand to show whether or not this is the case. But, as previously pointed out, neither the dorsal columns of the cord, nor their continuation as the medial lemniscus, establish any synaptic contact with the cells of the brain stem reticular formation or the intralaminar nuclei of the thalamus. On the other hand, ascending fibres from the antero-lateral quadrant of the cord (the so-called spino-thalamic tract or spinal lemniscus) has extensive connections with the reticular formation. As the total number of fibres in this bundle diminishes rapidly in its rostral course through the brain stem, it must be assumed that the reticular afferents are either independent axons or collaterals of direct spino-thalamic fibres which leave the parent axon low down in the cord.

It will be recalled that Ranson (1912) described a thin-fibred lateral part and a large-fibred medial part of the dorsal root of the spinal nerve at its point of entry into the posterior horn of the spinal grey matter in the cat. Ranson and Billingsley (1916) considered the thin-fibred lateral part of the root to be concerned with the conduction of painful and thermal impulses, while the thicker-fibred medial part was, in their opinion, a pathway for tactile and proprioceptive impulses. This teaching has been accepted with very little reinvestigation, although Ingvar (1927) was able to confirm that essentially the same anatomical situation exists in man. Recently Spivy and Metcalf (1959) have recorded evoked potentials in the midbrain reticular formation and the ventroposterior nucleus of the thalamus of the cat following stimulation of a lumbar nerve root. They were able to show that when the lateral division is cut, potentials still appear in the somatotopic thalamic nucleus, but not in the midbrain tegmentum; moreover they confirmed the original finding of Ranson and Billingsley (1916) that section of the lateral division abolishes the vasopressor response to peripheral nerve stimulation. Conversely, division of the medial part of the posterior root abolishes the thalamic

response, but does not affect the midbrain evoked potential of the vasopressor response.

These findings, together with the anatomical evidence, go far toward proving that the pathways from the spinal cord to the reticular formation and the intralaminar thalamic nuclei and from the spinal cord to the ventroposterior thalamic nucleus, are functions of independent fibre systems, and not of collateral branches from a single axon.

Other significant differences exist between the direct lemniscal systems and the afferents to the ascending reticular system and intralaminar thalamic nuclei. The former are somatotopically organized, projecting to specific points in the thalamus and thence to the cortex, and may indeed be regarded as a sort of telegraph system, as illustrated in the older textbooks. Afferents to the reticular system and intralaminar nuclei, on the other hand, show no such somatotopic organization. Thus a single unit in the reticular formation may respond to stimuli from all over the body, as has been repeatedly demonstrated by neurophysiologists; the same is true for the cells of the centre median of the intralaminar thalamic nuclei (Albe-Fessard and Kruger, 1959). Moreover, single reticular units may respond to stimuli of different sensory modality, as first shown by Adrian (1949) and Moruzzi and Magoun (1949).

The ascending reticular system cannot therefore be considered as being somatotopically organized, like the lemniscal systems, nor is it modality specific, as are the latter. Ervin and Mark (1959) have stimulated the ventro-posterior thalamic nucleus (the end station of the spinal and medial lemnisci) in conscious humans, and have found that this always induces well-localized paraesthesiae, but never pain. On the other hand, the responses evoked in the cat's centre median by Albe-Fessard and Kruger (1959) were produced only by nocigenic stimuli, and never by touch or joint movement. Such evidence as we possess, then, suggests that discriminative modalities (touch and kinaesthesia) are mediated by the lemniscal systems, while the non-discriminative modalities, particularly "second pain", are mediated by the reticular system. The great problem, to which there is as yet no glimmer of a solution, is how the central nervous system distinguishes between the various nondiscriminative sensory modalities of pain, heat and cold.

In the lemniscal systems, there is probably only one synapse interposed between the peripheral nerve and the ventroposterior nucleus of the thalamus. In the ascending reticular system, on the other hand, there are a variable number of synapses between the peripheral nerve and the intralaminar nuclei of the thalamus (fig. 3),

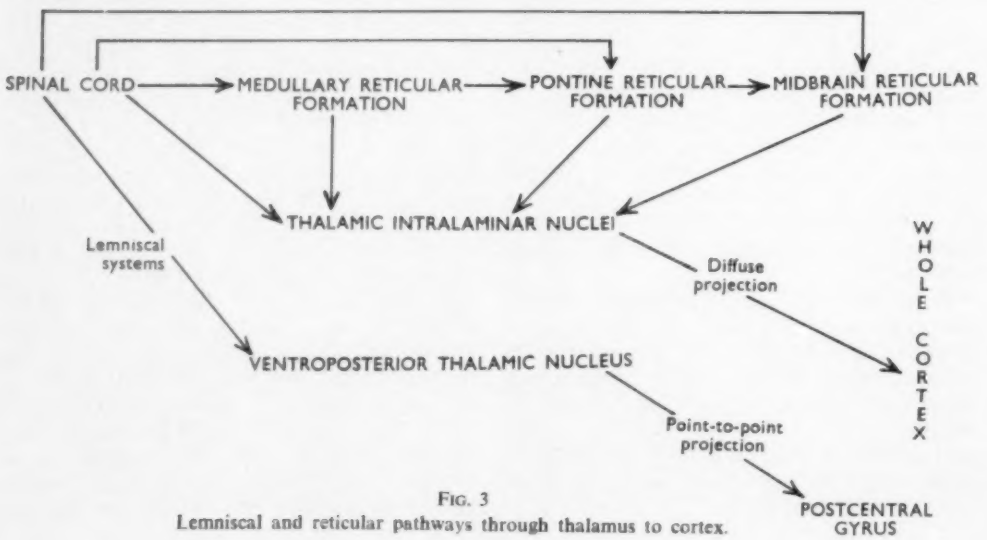


FIG. 3
Lemniscal and reticular pathways through thalamus to cortex.

a multiplicity of pathways being available. Thus a single shock delivered to a peripheral nerve will evoke a single response in the ventroposterior thalamic nucleus via the lemniscal systems, while a bombardment of impulses, spread out over a considerable period of time, will arrive at the intralaminar nuclei. These in turn project to the entire cortex by the diffuse thalamo-cortical circuits, and produce desynchronization of the resting e.e.g. pattern, again lasting over a period of time. In considering the significance of cortical desynchronization or arousal, we pass beyond the domain of functional anatomy into the borderland between physiology and psychology. But it should be stressed that it is essential to have an accurate picture of the ascending reticular system and its connections in anatomical terms before a correct assessment of its true function can be made.

REFERENCES

Adrian, E. D. (1949). The development of nerve cell rhythms. *Arch. Psychiat. Nervenkr.*, **183**, 197.

Albe-Fessard, D., and Kruger, L. (1959). Dualité des résponses des cellules du centre médian du thalamus à des stimulations naturelles ou électriques. *C. R. Acad. Sci.*, **248**, 299.

Allen, W. F. (1940). Distribution of the fibres originating from the different basal cerebellar nuclei. *J. comp. Neurol.*, **36**, 399.

Angeleri, F., and Carreras, M. (1956). Il problema delle connessioni corticali del nucleo ventrale anteriore del talamo dorsale. *Riv. Neurobiol.*, **2**, 645.

Bowsher, D. (1957). Termination of the central pain pathway in man: the conscious appreciation of pain. *Brain*, **80**, 606.

—— (1958). Projection of the gracile and cuneate nuclei in Macaca mulatta. An experimental degeneration study. *J. comp. Neurol.*, **110**, 391.

Brodal, A. (1957). *The reticular formation of the brain stem* (William Ramsey Henderson Trust lectures). Edinburgh: Oliver and Boyd.

—— Rossi, G. F. (1955). Ascending fibers in brain stem reticular formation of cat. *Arch. Neurol. Psychiat. (Chicago)*, **74**, 68.

Cajal, S. Ramon (1909). *Histologie du Système Nerveux de l'Homme et des Vertebrés*. Paris: Maloine.

Carrea, R. M. E., and Mettler, F. A. (1954). The anatomy of the primate brachium conjunctivum and associated structures. *J. comp. Neurol.*, **101**, 565

Collier, J., and Buzzard, E. F. (1903). The degeneration resulting from lesions of posterior nerve roots and from transverse lesions of the spinal cord in man. *Brain*, **26**, 559.

Ervin, F., and Mark, V. (1959). Physiological observations on the human thalamus. *Trans. Amer. Neurol. Ass.*, p. 94.

Perraro, A., Acella, B. L., and Barrera, S. E. (1940). Effects of lesions of the medial vestibular nucleus. An anatomical and physiological study in Macacus Rhesus monkey. *J. comp. Neurol.*, **73**, 7.

Getz, B. (1952). The termination of spinothalamic fibres in the cat as studied by the method of terminal degeneration. *Acta Anat.*, **16**, 271.

Glees, P. (1953). The central pain tract. *Acta neuroveg.*, **7**, 160.

—— Soler, J. (1951). Fiber content of the posterior column and synaptic connections of nucleus gracilis. Ztsch. f. Zellforsch., **36**, 381.

Gray, L. P. (1926). Some experimental evidence on the connections of the vestibular mechanism in the cat. *J. comp. Neurol.*, **41**, 319.

Hanbery, J., Ajmone-Marsan, C., and Dilworth, M. (1954). Pathways of non-specific thalamo-cortical projection system. *E.E.G. Clin. Neurophysiol.*, **6**, 103.

Hawkes, C. H. (1960). Personal communication.

Hewitt, W. (1959). The mammalian caudate nucleus. *J. Anat. (London)*, **93**, 169.

Hines, M. (1955). The anatomic basis for a new concept of the functional activity of the cerebral cortex in primates. *N. C. Med. J.*, **16**, 239.

Ingvar, S. (1927). Morphogenese der Tabes. *Acta med. scand.*, **65**, 645.

Jansen, J. (1954). *Efferent cerebellar connections*, in *Aspects of Cerebellar Anatomy*, ed. J. Jansen and A. Brodal, p. 232. Oslo: J. Grundt Tanum.

Jasper, H. H., and Ajmone-Marsan, C. (1950). Thalamo-cortical integrating mechanisms. *Res. Publ. Ass. nerv. ment. Dis.*, **30**, 493.

Johnson, T. N., and Clemente, C. D. (1959). An experimental study of the fiber connections between the putamen, globus pallidus, ventral thalamus and midbrain tegmentum in the cat. *J. comp. Neurol.*, **113**, 83.

Kohnstamm, O. (1899). Ueber Ursprungskerne spinaler Bahnen im Hirnstamm speciell über das Atemcentrum. *Arch. Psychiat. Nervenkr*, **32**, 681.

—— Quensel, F. (1908). Das Centrum receptorium (sensorium) der Formatio reticularis. *Neurol. Zbl.*, **27**, 1046.

Kuypers, H. G. J. M. (1958). An anatomical analysis of corticobulbar connexions to the pons and lower brain stem in the cat. *J. Anat. (Lond.)*, **92**, 198.

Lorente de Nò, R. (1933). Vestibulo-ocular reflex arc. *Arch. Neurol. Psychiat. (Chicago)*, **30**, 245.

Macchi, G., Angeleri, F., and Carreras, M. (1956). Le basi anatomiche del sistema talamico a proiezione diffusa. *Riv. Pat. Nerv. Ment.*, **77**, 895.

—— de Risio, C. (1954). Sui rapporti fra nucleo reticolare del talamo e corteccia cerebrale. *Att. Soc. Ital. Anat.*, **15**, 1.

Magoun, H. W. (1952). An ascending reticular activating system in the brain stem. *Arch. Neurol. Psychiat. (Chicago)*, **67**, 145.

—— McKinley, W. A. (1942). The termination of ascending trigeminal and spinal tracts in the thalamus of the cat. *Amer. J. Physiol.*, **137**, 409.

Matzke, H. A. (1949). Course of the fibers arising from nucleus gracilis and cuneatus of the cat. *Anat. Rec.*, **103**, 487.

Mehler, W. R., Feferman, M. E., and Nauta, W. J. H. (1956). Ascending axon degeneration following anterolateral chordotomy in the monkey. *Anat. Rec.*, **124**, 332.

Mettler, F. A., Grundfest, H., and Hovde, C. A. (1952). Distant electrical potentials evoked by stimulation of the caudate nucleus. *Anat. Rec.*, **112**, 359.
Morison, R. S., and Demsey, E. W. (1942). A study of thalamo-cortical relations. *Amer. J. Physiol.*, **135**, 281.
—— Finley, K. H., and Lothrop, G. N. (1943). Influence of basal forebrain areas on the electrocorticogram. *Amer. J. Physiol.*, **139**, 410.
Moruzzi, G., and Magoun, H. W. (1949). Brain stem reticular formation and activation of the E.E.G. *E.E.G. Clin. Neurophysiol.*, **1**, 455.
Nauta, W. J. H., and Kuypers, H. G. J. M. (1958). *Some ascending pathways in the brain stem reticular formation*, in *Reticular Formation of the Brain*, p. 3. Boston: Little, Brown & Co.
—— Whitlock, D. G. (1954). *An anatomical analysis of the non-specific thalamic projection system*, in *Brain Mechanisms and Consciousness*, p. 81. Oxford: Blackwell.
Olszewski, J., and Baxter, D. (1954). *Cytoarchitecture of the Human Brain Stem*. Basel: S. Karger.
Papez, J. W. (1956). Central reticular path to intralaminar and reticular nuclei of thalamus for activating E.E.G. related to consciousness. *E.E.G. Clin. Neurophysiol.*, **8**, 117.
Pearce, G. W., and Glees, P. (1956). The tectal projection to the brain stem reticular formation in the cat. *J. Anat. (Lond.)*, **90**, 599.
Petrén, K. (1910). Über die Bahnen der Sensibilität im Rückenmarke, besonders nach den Fällen von Stichverletzung studiert. *Arch. Psychiat. Nervenkr.*, **47**, 495.
Powell, T. P. S., and Cowan, W. M. (1956). A study of thalamo-striate relations in the monkey. *Brain*, **79**, 364.
Purpura, D. P., Housepian, E. M., and Grundfest, H. (1958). Analysis of caudate and cortical connections in neuraxially intact and télencephale isolé cats. *Arch. ital. Biol.*, **96**, 145.
Ranson, S. W. (1912). The structure of the spinal ganglia and of the spinal nerves. *Amer. J. Anat.*, **12**, 67.
Ranson, S. W., and Billingsley, P. R. (1916). The conduction of painful afferent impulses in the spinal nerves. Studies in vasometer reflex arc. II. *Amer. J. Physiol.*, **40**, 571.
Rose, J. E. (1952). The cortical connections of the reticular complex of the thalamus. *Res. Publ. Ass. nerv. ment. Dis.*, **30**, 454.
Rossi, G. F., and Brodal, A. (1956). Corticofugal fibers to the brain-stem reticular formation. An experimental study in the cat. *J. Anat. (London)*, **90**, 42.
—— —— (1957). Terminal distribution of spino-reticular fibers in the cat. *Arch. Neurol. Psychiat. (Chicago)*, **78**, 439.
Scheibel, M. E. (1955). Axonal efferent patterns in the bulbar reticular formation. *Anat. Rec.*, **121**, 362.
Simma, K. (1957). Der Thalamus der Menschaffen. *Psychiat. Neurol.*, **134**, 145.
Singer, M., and Yakovlev, P. I. (1954). *The Human Brain in Sagittal Section*. Springfield, Ill.: C. C. Thomas.
Spivy, D. F., and Metcalf, J. S. (1959). Differential effect of medial and lateral dorsal root sections upon subcortical evoked potentials. *J. Neurophysiol.*, **22**, 367.
Starzl, T. E., and Whitlock, D. G. (1952). Diffuse thalamic projection system in monkey. *J. Neurophysiol.*, **15**, 449.
Stotler, W. A. (1953). An experimental study of the cells and connections of the superior olivary complex of the cat. *J. comp. Neurol.*, **98**, 401.
Torvik, A. (1956). Afferent connections to the sensory trigeminal nuclei, the nucleus of the solitary tract, and adjacent structures. An experimental study in the rat. *J. comp. Neurol.*, **106**, 51.
—— Brodal, A. (1957). The origin of reticulo-spinal fibers in the cat. An experimental study. *Anat. Rec.*, **128**, 113.
Walker, A. E. (1939). The origin, course and termination of secondary pathways of the trigeminal nerve in primates. *J. comp. Neurol.*, **71**, 59.
—— (1940). The spinothalamic tract in man. *Arch. Neurol. Psychiat. (Chicago)*, **43**, 284.

Brit. J. Anaesth. (1961), 33, 183

BRAIN MECHANISMS FOR WAKEFULNESS

BY

H. W. MAGOUN

Department of Anatomy, School of Medicine, University of California, Los Angeles, U.S.A.

WHENEVER general anaesthesia is induced, the basic process involves a blockade of brain mechanisms subserving the waking state, knowledge of which has accumulated from a variety of investigative fields. Valuable information has come from study of normal wakefulness and sleep (Kleitman, 1939), as well as from disturbance of these states following injury to the brain (von Economo, 1929). Early instances have demonstrated behavioural arousal induced by central neural stimulation (Ranson and Magoun, 1939), but most rapid recent progress has depended upon observations of the electrical activity of the brain.

Study of the e.e.g. arousal or blocking reaction, in which large, slow waves, characteristic of the relaxed or sleeping record, are replaced by low-voltage, fast discharge during the alert or waking state, has in particular been rewarding. As Brazier's (1961) superb review shows, the e.e.g. was discovered by Caton as early as 1875, but the blocking action of arousing stimuli upon its resting rhythm was first noted by Beck (1905). "The oscillations," Beck wrote, "observed when two points of the cerebral cortex are connected to a galvanometer, cease as soon as any one of the afferent nerves is sufficiently strongly stimulated, and for as long as the stimulus is continued, even if the nerve excited doesn't correspond at all to the area of cortex examined."

These observations were confirmed by Neminsky (1913) who provided the first photographic record of the e.e.g. blocking reaction (fig. 1). In Neminsky's experiments, the sciatic nerve was stimulated in the curarized dog and "if appreciable 'spontaneous' fluctuations preceded stimulation, a reducing effect was clearly noticeable," although he "did not succeed in causing complete cessation of all fluctuations". A quarter-century later, in a study of afferent evocation of wakefulness in the sleeping cat, Rheinberger and Jasper (1937) found e.e.g. activation to be induced equivalently by several sensory modalities and, however elicited, to be distributed generally over the hemisphere, without predilection for the cortical area of the stimulus setting it into play. Additionally, this e.e.g. activation pattern, once initiated, persisted long after cessation of the brief arousing stimulus. These observations emphasized the importance of peripheral stimuli in provoking e.e.g. and behavioural wakefulness, but suggested the additional involvement of a central mechanism, the influence of which was more generalized and prolonged than that of activity in a specific afferent path.

At about the same time and independently, Bremer's (1937) attention became attracted to the previously unexplored behaviour of parts of the CNS lying ahead of transactions through the brain stem. Cortical electrical activity displayed a waking pattern, following bulbospinal section; while, after section through the midbrain, the record was that of sleep. A decade later, Professor G. Moruzzi, now Director of the Institute of Physiology at the University of Pisa, Italy, spent a year at the Northwestern University Medical School, Chicago, where collaborative study identified a corticipetal projection from the central core of the brain stem, between Bremer's two sections, which subserved wakefulness and through which the arousing effects of afferent stimulation were induced (Moruzzi and Magoun, 1949). Direct stimulation of the reticular formation of this central brain stem core reproduced all the electrocortical features of e.e.g. arousal and, as figure 2, from subsequent studies by Segundo, Arana-Iniguez and French (1955), shows, of behavioural wakefulness as well.

The significance for wakefulness of this excitable subcortical region was next explored by observing the consequences of its experimental

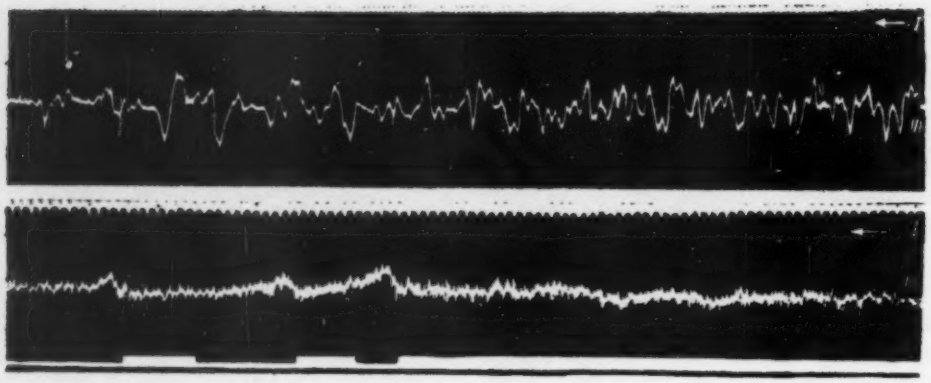


FIG. 1

The first published record of the e.e.g. arousal reaction, from Neminsky (1913). Above are seen the synchronous brain potentials of a curarized dog during drowsiness and, below, the desynchronized e.e.g. during arousal induced by repeated stimulation of the sciatic nerve. The records read from right to left: line one being a time-marker in fifths of a second; line three, the galvanometers string; and the signal at the bottom marking stimulation of the sciatic nerve.

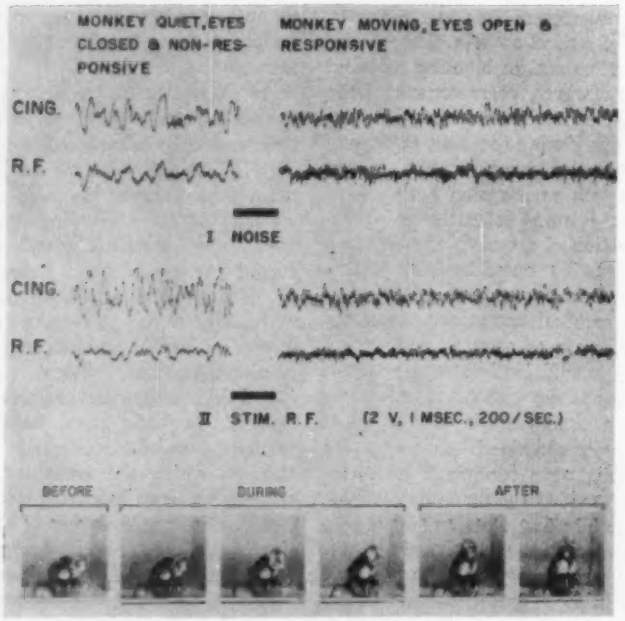


FIG. 2

Electrical activity of the monkey's cingulate cortex and reticular formation recorded with implanted electrodes, together with frames from a motion-picture, below, showing e.e.g. and behavioural arousal evoked by acoustic (1) or reticular (2) stimulation. (From Segundo, Arana-Iniguez and French, 1955.)

injury. During periods of survival from 2 to 4 weeks, monkeys with large lesions of the central cephalic brain stem remained as though deeply asleep or anaesthetized. Their e.e.g.'s were composed of large, slow waves and, though the long sensory and motor paths to and from the cortex were intact, neither behavioural nor e.e.g. arousal could be induced by intense peripheral stimulation. By analogy with clinical states following lesions in this same subcortical region of the brain in man, these animals could be described as comatose.

Conclusions from briefly surviving animals require modification, however, because of the recent work of Batsel (1960), who succeeded in preserving dogs with isolated cerebral hemispheres for periods of months. After the first month, the e.e.g. of such a "cerveau isolé" shifted from continuous synchronization, characteristic of sleep, to a prolonged pattern of wakefulness. In one of Batsel's dogs with aspiration of the midbrain (fig. 3), the recurring spindle bursts and slow waves, seen 2 weeks after operation, were suc-

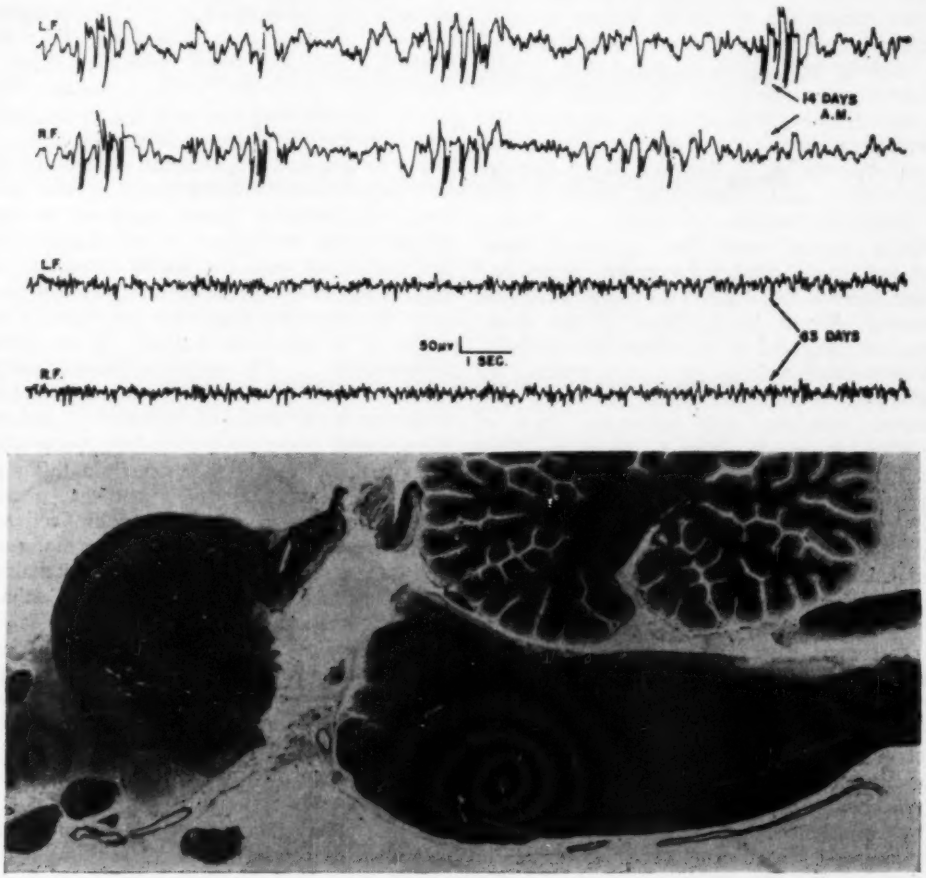


FIG. 3

E.e.g. records taken on the fourteenth day (above) and sixty-third day (below), after chronic isolation of the cerebral hemisphere of the dog by aspiration of the midbrain (photomicrograph from Batsel, 1960).

ceeded, at 9 weeks, by long periods of low, fast discharge. Neither the optic nor olfactory nerves contributed essentially to this activated pattern; it still developed if the optic nerves were cut prior to midbrainectomy, while olfactory stimuli never induced arousal changes in chronic preparations displaying synchronized patterns. Batsel (1960) concluded that "there is an inherent but variable tone, located somewhere within the cephalic extent of the activating system, which remains connected with the cerebral cortex".

The incapacity of any of the modalities of afferent stimulation to induce arousal in such preparations with large lesions or transections of the cephalic brain stem suggested that sensory influences upon wakefulness are normally exerted through extralemniscal channels, involving the central brain stem core, rather than by the way of direct pathways to the cortex. In acute preparations without central anaesthesia, activity evoked by peripheral somatic or auditory stimulation could be recorded widely from the central brainstem and usually displayed a greater latency and longer duration than that in the direct path. This collateral afferent bombardment of the brainstem core appeared to be transmitted cephalically by multiple reticular relays, with evidence for convergence of input from different sources upon common elements, and consequent lack of modality segregation (French, Hernandez-Peon and Livingston, 1955). More recent, unit-recording studies, such as that of figure 4, from Bradley and Mollica (1958), illustrate the increased discharge of a single mesencephalic unit induced by stimulation of all four legs or face, as well as by acoustic stimulation. While augmented frequency of unit-firing and recruitment of quiescent elements seemed most to characterize the arousal process in the brain stem, inhibition or lack of influence upon unit activity was also seen (Machne, Calma and Magoun, 1955). Moreover, alterations in the burstlike patterns of discharge, suggesting the possibility of coding, may be of significance. Such electrophysiological studies have also shown that, in addition to sensory sources, most of the central components of the brain, including the cerebellum, limbic system, basal ganglia and neocortex make functional connections with the brain stem core and are able to influence its performance.

The manifold sources of its input, together with the global efferent influences of this brain stem core—exerted cephalically upon the cortex and deep-lying mechanisms of the hemisphere, as well as caudally upon afferent relays and skeletal or visceral motor outflows of the cord—are probably responsible for the adjectives "nonspecific" and even "indiscrete", sometimes applied to the organization and function of this portion of the brain. There is increasing indication, however, that in spite of its multiple neural interrelations, the reticular system is able to subserve discriminative and differentiated, as well as generalized, activities. Sharpless and Jasper (1956) have distinguished tonic and phasic levels of function in the reticular formation. In their words: "The more caudally situated reticular system is capable only of crude differentiation between stimuli and produces long-lasting persistent changes in the level of reactivity. The properties of the lower brain stem reticular system, therefore, are well suited to the maintenance of wakefulness over long periods of time, but are ill adapted to the sudden and brief changes in reactivity that must occur in response to highly specific stimuli, if the animal is to meet the demands of its waking environment. . . . The unspecific thalamic system is strategically situated for subserving attentive processes in the conscious animal . . . and has physiological properties distinct from those of the lower reticular activating system." In this same vein, Anokhin (1961) points out that a nonspecific mechanism which invariably activated the entire hemisphere would deprive the cortex of its most characteristic ability, to discriminate and form selective associations. During elaboration of conditional reflexes of opposite sign, involving defensive and alimentary behaviour, Anokhin has observed qualitatively different types of electrical activity and, with chlorpromazine, has been able to induce differential block of responses to defensive conditioned stimuli while the animal remained awake, searched for and ate its food greedily.

These observations raise the question of what is known concerning the intimate physiology of the electrocortical alteration called e.e.g. arousal. A striking recent development of general neurophysiology has been the discovery of a relatively slow, graded, chemically mediated mechanism

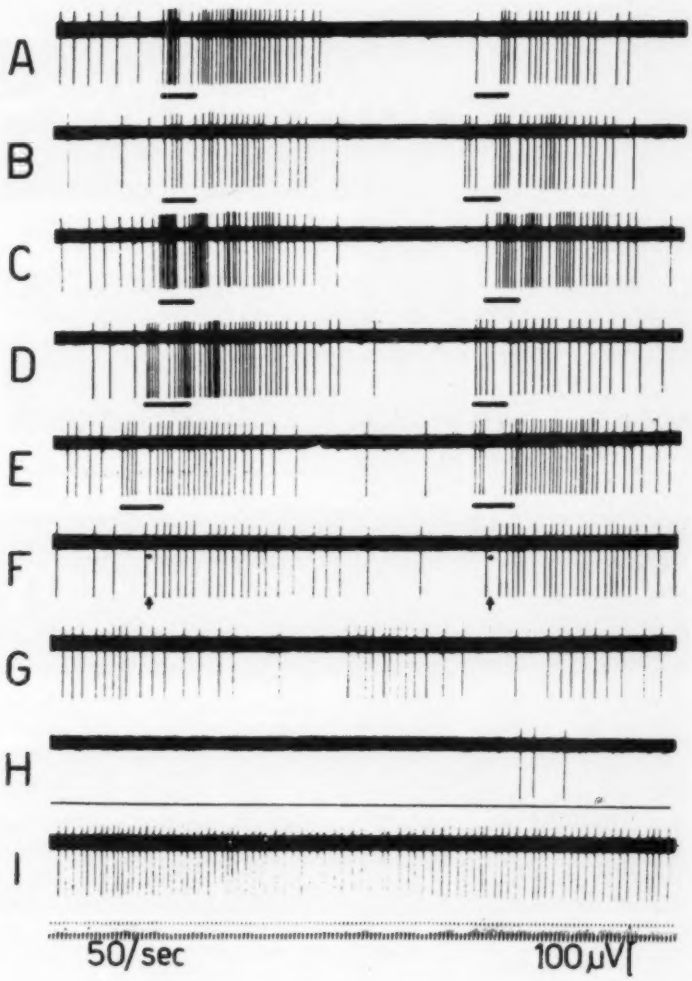


FIG. 4

Records of the activity of a single neuron unit in the midbrain of the decerebrate cat showing convergence of responses: A, tapping the right front leg; B, tapping the left front leg; C and D, tapping right and left hind legs; E, touching the nose; F, acoustic stimulation with clicks; G and H, inhibition produced by cerebellar polarization, and I, rebound. (From Bradley and Mollica, 1958.)

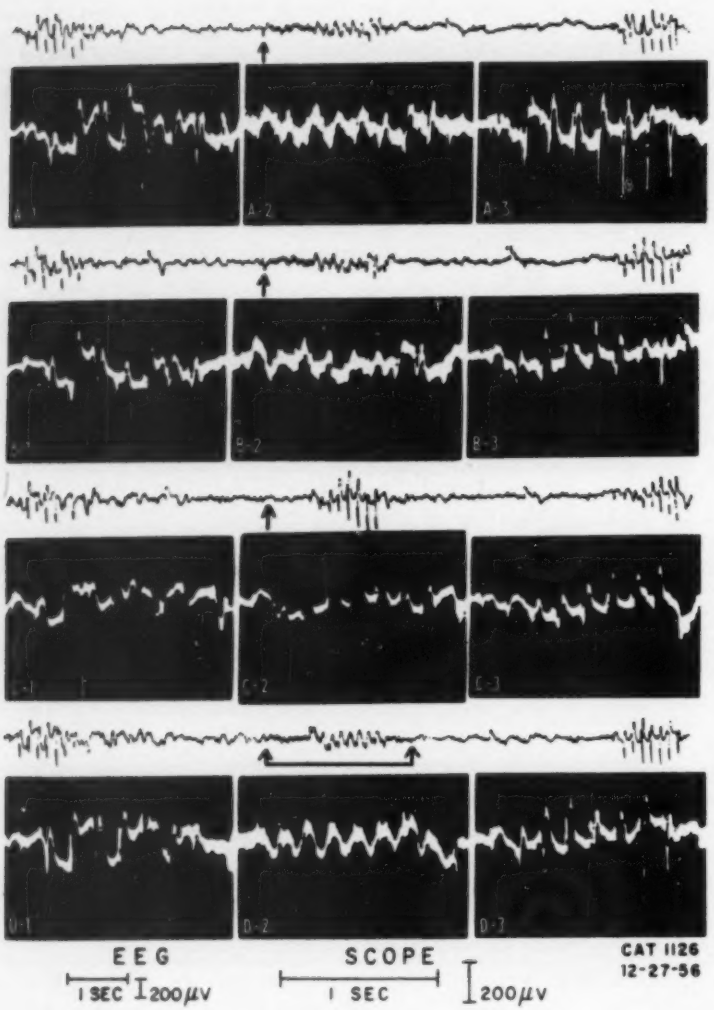


FIG. 5

Ink-written and oscilloscope traces of responses recorded in the anterior suprasylvian gyrus with implanted electrodes during stimulation of the thalamic nucleus centremedian in the waking cat (left and right columns A to D, 1 and 3). In the middle column of records note a blockade of responses when a noise attracted the animal's attention (A and B-2), but not when it was ignored after repetition (C-2). Compare the blockade of responses during reticular stimulation, at the bottom (D-2). (From Evarts and Magoun, 1957.)

of excitation at terminal, receiving or transmitting neuronal processes, the properties of which differ from the brief, electrically managed, all-or-none excitation, characteristic of the conducting axonal portion of the neuron. Dendritic processes, forming such an obtrusive feature of the superficial layers of the cortex, have received special emphasis in this connection, and the surface-negative components of the local cortical, recruiting, augmenting, transcallosal or other evoked responses are now attributed to postsynaptic, dendritic depolarization. Such surface-negative, cortical responses are characteristically observed to be reduced or abolished during e.e.g. arousal, and Purpura (1956) has, therefore, concluded that electrocortical activation is "primarily associated with an inhibition of evoked dendritic activity". As an illustrative instance, figure 5 shows the manner in which surface-negative recruiting responses, evoked by low-frequency thalamic stimulation, are blocked during e.e.g. arousal, whether induced by sensory or direct reticular stimulation (Evarts and Magoun, 1957). These changes are now known to be associated with a DC shift of the affected cortical region (Brookhart et al., 1958), and the degree to which this is also importantly involved still remains to be determined.

Since practically all complex behaviour occurs during wakefulness, rather than in sleep, it might be presumed that e.e.g. arousal should favour rather than impair some features of cortical excitability and performance. The recent observations of Dumont and Dell (1958) and of Bremer and Stoupel (1959) have provided striking demonstration that this is so. Both groups find that brain stem reticular excitation can exert a powerful facilitation upon cortical responses induced by exciting the thalamic nuclei or optic nerve. In the instances seen in figure 6, from Dumont and Dell (1958), visual cortical responses to threshold afferent stimulation display prodigious and prolonged facilitation during reticular excitation, the later phases of the responses, including those attributed to dendritic depolarization, showing the greatest increase in amplitude and duration. Although characteristically associated with activation of the e.e.g. this facilitation can still occur when such e.e.g. changes are blocked by anaesthesia or by atropine. Recent single-neuron studies have shown

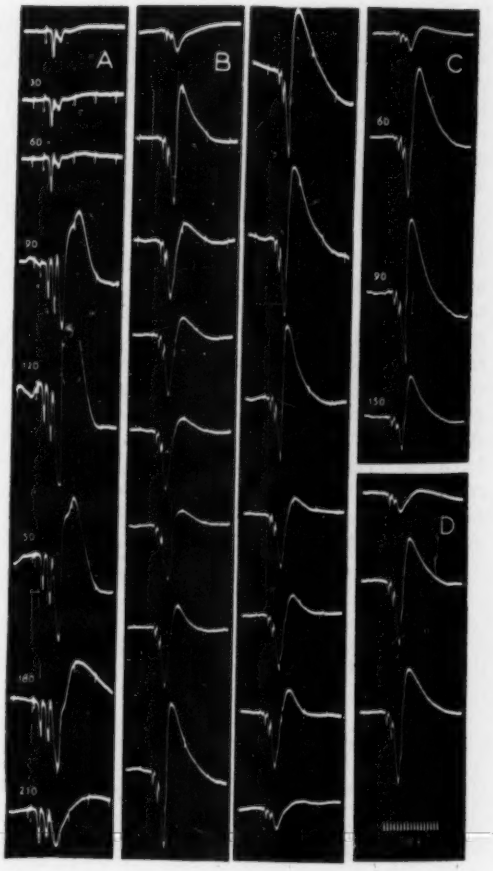


FIG. 6.

Examples of facilitation of the visual cortical response to a chiasmatic shock during reticular and other arousing stimulation in the "encéphale isolé" cat. The control response, before reticular stimulation is shown at the top of each of the vertical columns of records, A, B, C, and D.

In A, the chiasmatic shock follows 30, 60, 90, 120, 150, 180 and 210 m.sec after the beginning of reticular stimulation.

In B, the records are taken at 3 sec intervals during a period of prolonged reticular stimulation.

In C, facilitation results from a loud click given 60, 90 and 150 m.sec before the chiasmatic shock.

In D are two examples of facilitation of the visual response induced by a period of stimulation of the median nerve in a preparation with spinal section at T2.

(From Dumont and Dell, 1958).

instances of increased cortical unit activity, displayed as repetitive discharge, during e.e.g. arousal and wakefulness (Evarts, 1960), but more common findings include the smoothing out of burst-discharge, with a marked increase in regularity but no overall change in the rate of cortical firing (Hubel, 1959), or a reduction of spontaneous or evoked discharge (Evarts, 1960).

From the material so far presented, it is clear that earlier study of e.e.g. arousal and wakefulness has focused upon the role of afferent stimulation and of influences exerted by the central brainstem upon the cortex. During the past decade, however, study has included additional attention to influences, exerted reciprocally, by the cortex upon the brain stem core. A number of cortical regions has been found to be involved (Jasper, Ajmone-Marsan and Stoll, 1952), and their collective projections form an input to the arousal mechanism of a variety and volume second in importance only to that from peripheral receptors. As seen in figure 7, from Bremer and Terzuolo (1953), generalized e.e.g. arousal can be induced by exciting these corticoreticular projections. As illustrated in figure 8, French, Hernandez-Peon and Livingston (1955) have found that cortical areas with special effectiveness include cingulate, orbital and lateral frontal regions, central and para-occipital areas, and the superior gyrus and tip of the temporal lobe. Excitation of these cortical areas awakens the sleeping animal, just as does exciting peripheral receptors or the subcortical reticular system (Segundo, Naquet and Buser, 1955); and the facilitatory or blocking interaction of their influence upon reticular activity has been analyzed by Adey, Segundo and Livingston (1957). The e.e.g. pattern of wakefulness observed in the chronic "cerveau isolé" (fig. 3) may be attributed to activity developing between these cortical regions and diencephalic components of the reticular system.

The significant role of these cortical mechanisms has recently been emphasized by Sokolov (1960) in a synthesis of studies on the orienting

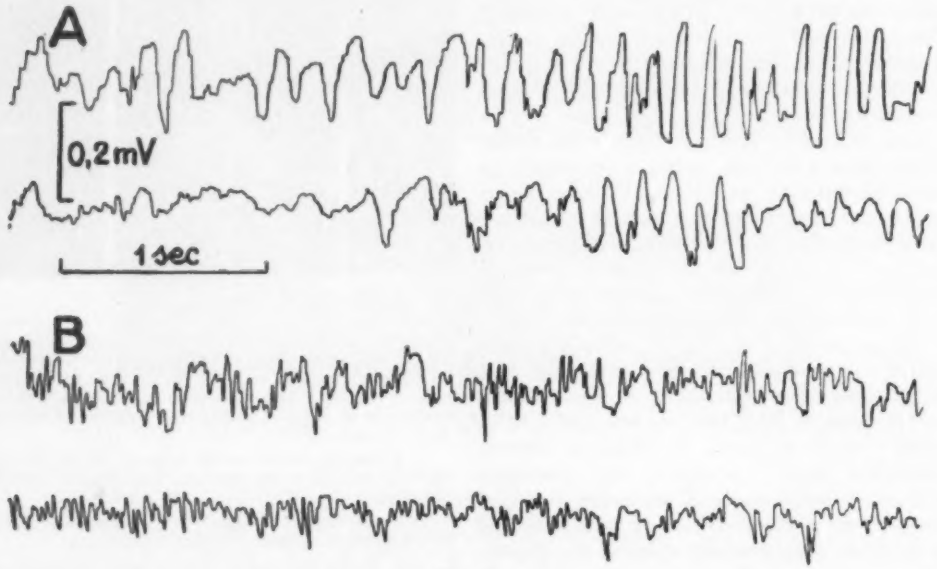


FIG. 7

Records of the electrical activity of the left posterior suprasylvian gyrus (upper) and primary auditory area (lower channel) in the "encephale isolé" cat, with section of the corpus callosum. (A) during spontaneous sleep; (B) during wakefulness provoked by 1 sec of repetitive stimulation of the right paravisual area, immediately before (B). (From Bremer and Terzuolo, 1953.)

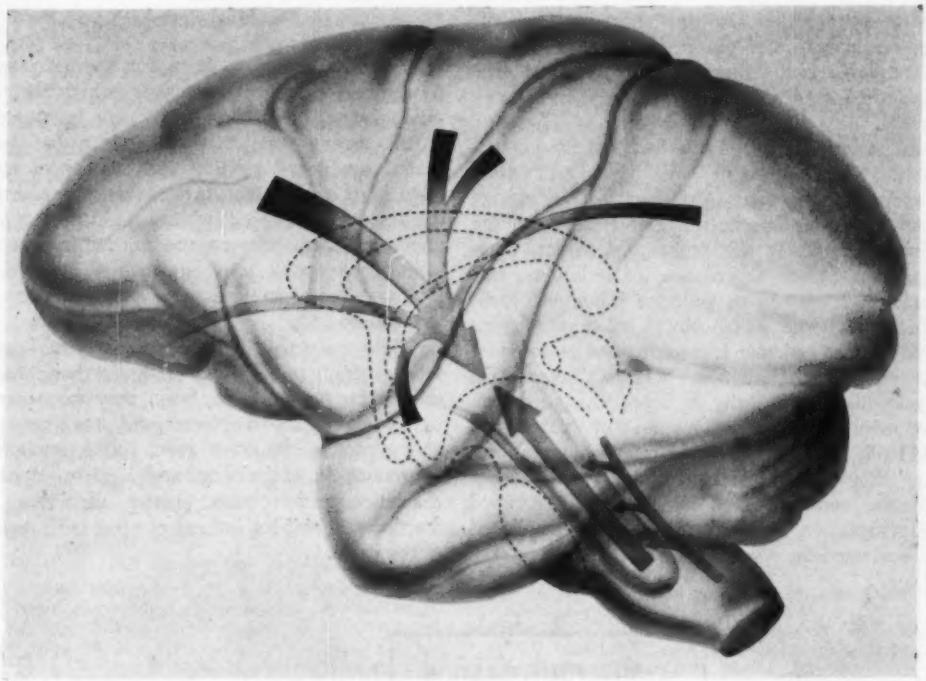


FIG. 8

Lateral view of the monkey's brain showing interconnections of the cerebral cortex and brainstem core. The ascending reticular system receives collaterals from afferent paths and projects (not shown) to the same cortical regions from which corticifugal paths descend to the central brain stem. (From French, Hernandez-Peon and Livingston, 1955.)

reflex; which includes somatic and visceral, as well as e.e.g. alterations, the latter corresponding to the e.e.g. arousal reaction of Western terminology. These responses enhanced the discriminatory power of the analyzers, enabling them to gain more information about the unusual properties of the evocative stimulus, and so prepare the subject for dealing more effectively with it. As Razran (1961) points out, unlike other reaction patterns of the organism, those of the orienting reflex do not manage the stimuli initiating them, but are merely reactive to their presence; these reaction patterns are thus more preparatory than consummatory, and are preadaptive rather than adaptive in nature. Its typical induction by nonstereotyped stimuli suggests that the orienting reflex is not initiated directly by the stimulus, in the customary sense, but rather is induced by a change in the modality, intensity, temporal pattern, or other parameter of stimulation.

The concept of a cortical neuronal model has been proposed by Sokolov (1960) to account for this induction of the orienting reflex by stimuli whose novelty is their characteristic feature. This neuronal model is conceived as a cell assembly which preserves information about the qualities or parameters of earlier stimuli, with which analogous aspects of current stimulation may be compared. According to the hypothesis, the orienting reflex is evoked whenever, upon such comparison, features of the current stimulus do not coincide with those of the established neuronal model. This discordance is proposed to generate corticifugal discharge to the brain stem reticular system, the increased activity of which evokes

the orienting reflex. In this scheme, therefore, major significance is attached to cortical control of reticular excitability, as distinct from that proceeding more directly from peripheral receptors.

In the contrasting situation, when current stimuli are coincident with the established neuronal model, there is no excitatory discharge from the cortex to the reticular system and the orienting reflex is not evoked. Moreover, upon repetition, such accordance of stimulus and model is suggested to generate inhibitory corticifugal discharge, which blocks collateral afferent input to the reticular formation, and so provides the basis for habituation. Sokolov's hypothesis, shown diagrammatically in figure 9, is thus seen to involve the participation of subcortical mechanisms in the orienting reflex, but proposes that they are importantly subject to corticoreticular control, which is, in turn, determined by comparison of novel stimuli with established cortical models.

SUMMARY

When one attempts to formulate generalizations concerning neural mechanisms subserving the waking state, major significance can be attached to the central brainstem core which has been found capable of grading the activity of most other parts of the brain. It does this as a reflection of its own internal excitability, in turn a consequence of both afferent and corticifugal neural influences, as well as of the titre of humoral or pharmacological substances in its parenchyma or circulation.

While the activities of this nonspecific system tend generally to be more widespread than those of the specific systems of the brain, they are proposed to be divided into a coarser and more tonically acting part in the lower stem, subserving global alterations in excitability, and a more cephalic, thalamic portion with greater capacities for fractionated, shifting influences upon focal regions of the brain.

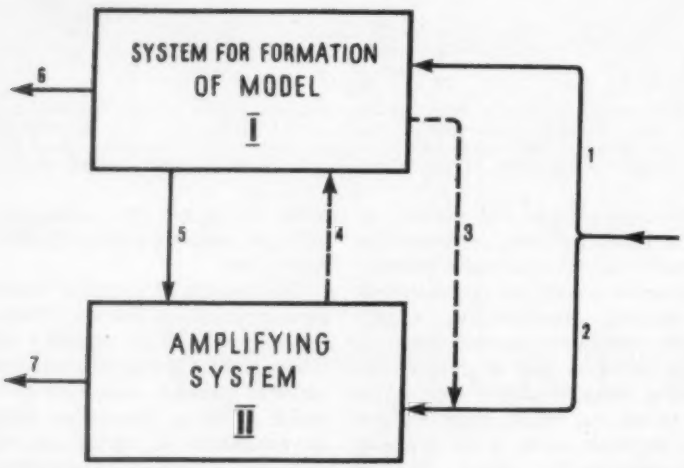


FIG. 9

Schema for the interrelations of the cortex (I) and brain stem (II) in the orienting reflex. Numerals are as follows: 1, specific afferent path to cortex; 2, reticular collateral; 3, negative feedback from cortex to reticular collateral relay; 4, ascending reticular activating system; 5, corticoreticular path; 6, to outflows for specific responses evoked by matching input with cortical model; 7, path to vegetative and somatic outflows in orienting reflex. (From Sokolov, 1960.)

It was previously assumed that influences exerted by this subcortical mechanism upon the cerebral cortex served to initiate and maintain wakefulness in appropriate relation to the external world, while reciprocal influences from the cortex to the stem functioned similarly in relation to internal activity of the brain. More recently, it has been proposed that all neural input is first conveyed to the cortex for comparison there with neuronal models established by previous stimulation. Succeeding corticifugal discharge to the central brainstem core, excitatory if the match is discordant and inhibitory if it is accordant, is suggested to induce arousal and the orienting reflex, or habituation, respectively. Among the attractions of this proposal is the ready explanation it affords for the arousing qualities of novel and the soporific qualities of monotonous stimulation so apparent in reading the scientific literature, and in many other fields.

REFERENCES

Adey, W. R., Segundo, J. P., and Livingston, R. B. (1957). Corticifugal influences on intrinsic brain stem conduction in cat and monkey. *J. Neurophysiol.*, **20**, 1.

Anohkin, P. K. (1961). Some new findings relating to the functional heterogeneity of the reticular formation in the brain stem. Pavlovian Conference on Higher Nervous Activity. *N.Y. Acad. Sci.* (in press).

Batsel, H. L. (1960). Electroencephalographic synchronization and desynchronization in the chronic "cerveau isolé" in the dog. *EEG clin. Neurophysiol.*, **12**, 421.

Beck, A. (1905). Electrical phenomena of the brain cortex after its partial destruction. A contribution to the localization of the sensation of pain (in Polish). *Rozpr. Wydz. mat-przyr. Polsk. Akad. Um.*, Series III, 5B, 319.

Bradley, P. B., and Mollica, A. (1958). The effect of adrenaline and acetylcholine on single unit activity in the reticular formation of the decerebrate cat. *Arch. ital. Biol.*, **96**, 168.

Brazier, M. A. B. (1961). *The Electrical Activity of the Brain: A Half-Century of History.* New York: MacMillan Co. (in press).

Bremer, F. (1937). L'activité cérébrale au cours du sommeil et de la narcose. Contribution à l'étude du mecanisme du sommeil. *Bull. Acad. roy. Méd. Belg.*, **2**, 68.

—— Stoupel, N. (1959). Facilitation et inhibition des potentials evoques corticaux dans l'éveil cérébral. *Arch. int. Physiol.*, **67**, 240.

Bremer, F., and Terzuolo, C. (1953). Nouvelles recherches sur le processus physiologique de revéil. *Arch. int. Physiol.*, **61**, 86.

Brookhart, J. M., Arduini, A., Mancia, M., and Moruzzi, G. (1958). Thalamo-cortical relations as revealed by induced slow potential changes. *J. Neurophysiol.*, **21**, 499.

Dumont, S., and Dell, P. (1958). Facilitations specifiques et nonspecifiques des reponses visuelles corticales. *J. Physiol.* (Paris), **50**, 261.

Economo, C. von. (1929). *Die Encephalitis lethargica; ihre Nachkrankheiten und ihre Behandlung.* Berlin: Urban and Schwarzenberg.

Evarts, E. V. (1960). Effects of sleep and waking on spontaneous and evoked discharge of single units in visual cortex. *Fed. Proc.*, **19**, 828.

—— Magoun, H. W. (1957). Some characteristics of cortical recruiting responses in unanesthetized cats. *Science*, **125**, 1147.

French, J. D., Hernandez-Peon, R., and Livingston, R. B. (1955). Projections from cortex to cephalic brain stem in monkey. *J. Neurophysiol.*, **18**, 74.

—— Verzeano, M., and Magoun, H. W. (1953). An extralemniscal sensory system in the brain. *Arch. Neurol. Psychiat.* (*Chicago*), **69**, 505.

Hubel, D. W. (1959). Single unit activity in striate cortex of unrestrained cats. *J. Physiol.* (*Lond.*), **147**, 226.

Jasper, H. H., Ajmone-Marsan, C., and Stoll, J. (1952). Corticofugal projections to the brain stem. *Arch. Neurol. Psychiat.* (*Chicago*), **67**, 155.

Kleitman, N. (1939). *Sleep and Wakefulness.* Univ. of Chicago Press.

Machne, X., Calma, I., and Magoun, H. W. (1955). Unit activity of central cephalic brain stem in EEG arousal. *J. Neurophysiol.*, **18**, 547.

Moruzzi, G., and Magoun, H. W. (1949). Brain stem reticular formation and activation of the EEG. *Electroenceph. clin. Neurophysiol.*, **1**, 455.

Neminsky, W. W. (1913). Ein Versuch der Registrierung der elektrischen Gehirnerscheinungen. *Zbl. Physiol.*, **27**, 951.

Purpura, D. P. (1956). Observations on the cortical mechanisms of EEG activation accompanying behavioral arousal. *Science*, **123**, 804.

Ranson, S. W., and Magoun, H. W. (1939). The hypothalamus. *Ergebn. Physiol.*, **41**, 56.

Razran, G. (1961). A survey of experiments in interoceptive conditioning, semantic conditioning and the orienting reflex. *Psychol. Rev.* (in press).

Rheinberger, M. B., and Jasper, H. H. (1937). The electrical activity of the cerebral cortex in the unanesthetized cat. *Amer. J. Physiol.*, **119**, 186.

Segundo, J. P., Arana-Iniguez, R., and French, J. D. (1955). Behavioral arousal by stimulation of the brain in the monkey. *J. Neurosurg.*, **12**, 601.

—— Naquet, R., and Buser, P. (1955). Effects of cortical stimulation on electrocortical activity in monkeys. *J. Neurophysiol.*, **18**, 236.

Sharpless, S., and Jasper, H. H. (1956). Habituation of the arousal reaction. *Brain*, **79**, 655.

Sokolov, E. N. (1960). Neuronal models and the orienting reflex. In *The Central Nervous System and Behavior.* New York: Macy Foundation.

Brit. J. Anaesth. (1961), **33**, 194

SOME EFFECTS OF ANAESTHESIA ON THE BRAIN*

BY

MARY A. B. BRAZIER

Brain Research Institute, University of California, Los Angeles, and Center for Communication Sciences, Massachusetts Institute of Technology, Cambridge, U.S.A.

WHAT is anaesthesia? Is it failure of the brain to receive impulses from sensory stimuli; a failure of arriving sensory impulses to pass on into storage; or a failure of arriving sensory impulses to evoke affect? Are there levels of anaesthesia where all three of these failures take place and other levels at which they can be fractionated?

Not very long ago the answer seemed simple to the physiologist who would have replied that anaesthesia is caused by a deafferentation of the brain. In laboratory experiment this concept would appear to be borne out because surgical deafferentation of the brain at the collicular level results in an animal that cannot immediately be aroused (Bremer, 1935).

However, during the past decade there has been a growing recognition among neurophysiologists that the great systems within the brain have different major functions, all having some bearing on the problem of consciousness. That these individual functions can be differentially studied by the appropriate use of anaesthetic agents is one of the most promising potentials for research in this field.

The outstanding contribution that fundamentally changed all previously held concepts of the physiology of consciousness was the observation of Moruzzi and Magoun (1949) that repetitive excitation of the reticular formation in the central core of the brain stem induced e.e.g. arousal. The later expansion of this initial discovery and its implications for the states of vigilance and sleep form the subject of another chapter in this volume, but for those interested in anaesthesia it immediately became clear that loss of consciousness was likely to be caused more by blockade of the afferent systems in the central core than by deafferentation of the lateral classical sensory paths.

Electrolytic lesions confined to the reticular formation result in long lasting coma (French and Magoun, 1952; Lindsley et al., 1950), whereas lesions sparing the midline structures, but intercepting the classical sensory pathways in the brain stem, do not affect the sleep–waking cycle. Early experiments clearly indicated some role of this system in the reversible blockade produced by anaesthesia (French and Magoun, 1952; French, Verzeano and Magoun, 1953; King, 1956; King, Naquet and Magoun, 1957). These studies showed that single impulses entering by sensory nerves reached the cortex serially—first by the fast conducting specific pathways and then 8 to 12 m.sec later by the more slowly conducting central route. Transmission in this latter route was shown to be extremely vulnerable to barbiturate narcosis.

An example from the visual system is shown in figure 1 in which the average of several responses is depicted. This computer technique—which has been described elsewhere (Barlow, 1957)—was used because the waveform of single responses could not be detected in the background e.e.g. activity of the unanaesthetized animal. The short latency response that travels up the classical pathways is present in both the lateral geniculate nucleus and the visual cortex in the normal animal and persists at this level of anaesthesia. The response that follows 12 m.sec later comes from the reticular formation and bypasses the geniculate nucleus. It is abolished by the barbiturate.

As this work unfolded, some of the paradoxes that had plagued the electrophysiologist began to find their explanation. One was the general experience that, as already seen, a clear-cut electrical response to peripheral stimulation could be

* Aided by grants from the United States Public Health Service (B-369) and the Office of Naval Research, U.S. Navy (NR-101-445).

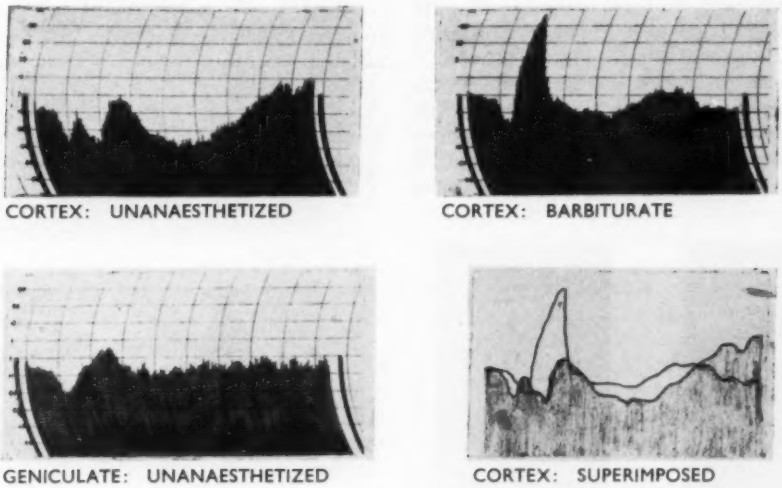


FIG. 1

Waveform of averaged responses to a flash computed in 1 m.sec steps.

Left, above: Cortical responses from implanted electrodes in an unanaesthetized cat showing initial surface-positive (downward) deflection beginning at 12 m.sec after the flash. Development of surface-negative wave broken into by another surface positive wave beginning 24 m.sec after flash.

Left, below: Simultaneous recording from lateral geniculate nucleus. Only the primary response is seen, the second having presumably travelled from the reticular formation by an extrathalamic route to the cortex.

Right, above: Pentobarbitone anaesthesia induced in the same cat abolishes all but the primary response, the principal site of action of the barbiturates being in the reticular formation.

Right, below: The envelopes of the averaged cortical responses, with and without anaesthesia have been superimposed for contrast. Note longer latency with barbiturate.

From: Brazier, M. A. B., *The Electrical Activity of the Nervous System* (2nd ed.), 1960. London: Pitman. New York: Macmillan.

recorded from the cortex even in relatively deep barbiturate anaesthesia. In fact, in this condition, the response could be more clearly seen because the background e.e.g. potentials were now depressed. With the elucidation of the role of the ascending influence from the reticular formation, it became clear that the latter, obtunded by the barbiturate, depressed the background e.e.g. to a degree that the relatively unaffected classical systems were now thrown into prominence.

Another paradox had arisen from the discovery of Derbyshire, et al. (1936), and the later studies of Forbes and Morison (1939) that as barbiturate anaesthesia deepened, a "new" late response developed about 80 to 100 m.sec after the first one. The latter they named "the secondary discharge", for the anaesthetic hid from them the midline conducted response that has just been described. They showed this late response to follow an ascending route distinct from the lemniscal pathway and to enter the internal capsule from the subthalamus. Originally demonstrated in the somatic system, the secondary response of long latency evocable in barbiturate narcosis has since been demonstrated in the

visual system and is probably general to all sense modalities (fig. 2) (Brazier, 1954a, b, c; Brazier, 1957)

In the case of electrical stimulation of the somatic system, Forbes and his group (1939) described the secondary discharge as a generalized response recordable all over the cortex. In the visual system, with flash as the stimulus, no such generalization has been found. Secondary responses to retinal illumination have so far been detected only in the visual cortex (Brazier, 1957).

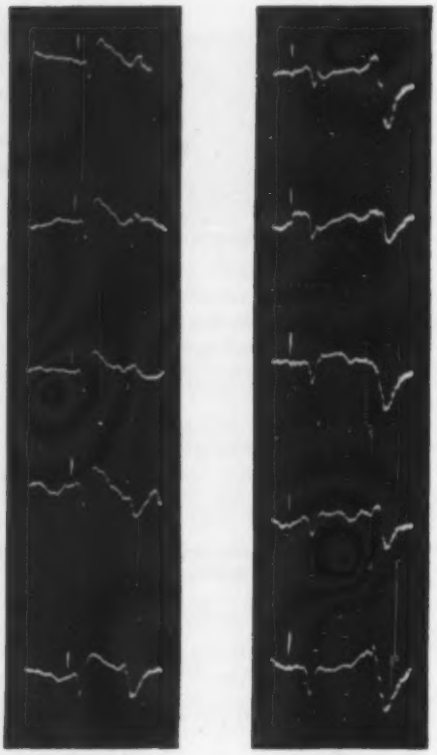


FIG. 2

The response to flash recorded from the visual cortex of a cat during gradually increasing depth of pentobarbitone anaesthesia. Note the constancy of amplitude but increasing latency of the primary response and the striking growth in both amplitude and latency of the Forbes "secondary" response. Flash occurs at the white mark. Time-line 100 c/s.

From: Brazier, M. A. B. (1954), in *Neuropharmacology*, Abramson, Ed. New York: Josiah Macy Jr. Foundation.

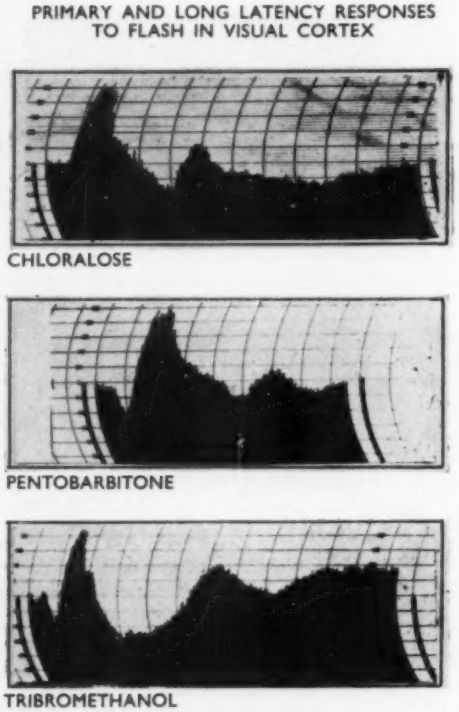


FIG. 3

Primary and long-latency (Forbes) responses recorded in the same cat under three different types of anaesthesia. In this cat the peaks of the late response occur with the latencies of 95 m.sec in chloralose, 110 m.sec in pentobarbitone and 120 m.sec in tribromethanol.

(Note: These curves represent the average waveform of 50 responses as determined by the computer described by Barlow (1957). The three pen deflections that stand alone at the beginning and end are for calibration only. The flash occurred at the first pen stroke of the continuous curve which is plotted in 1 m.sec steps.)

Usually described as being a "new" response brought in by the anaesthetic, the secondary response is nevertheless present in the unanaesthetized animal where it has a latency of 50–55 m.sec. Its amplitude is, however, usually so much less than that of the on-going e.e.g. activity that some technique (such as has been applied in figure 3) needs to be used for the averaging of

several responses, with the omission of potentials unrelated to the flash. The secondary response can also be detected by this means in chloralose or ether anaesthesia, but the phenomenon of its enhancement is essentially a feature of barbiturate action, a release from inhibition of a long latency path by suppression of the reticular pathway for short latency responses.

The long-latency secondary response of Forbes can be brought out, magnified or decreased by appropriate manipulation of the anaesthetic level, not only at the cortex (Forbes et al., 1949) but also in the hypothalamus and brain stem (Feldman and Porter, 1960).

This observation led to the suggestion that at a certain stage of narcosis the barbiturate might be blocking an inhibitory ascending system whose removal unleashed the secondary response in a long-latency pathway (Brazier, 1954b, c; Purpura, 1955). This effect is not only demonstrable in responses recorded directly from the exposed cortex of animals, but can be seen in recordings from scalp electrodes on man (see, for example, figure 4).

Evidence for an ascending inhibitory, as well as an ascending excitatory influence from the reticular formation began to accumulate from several sources. The micro-electrode studies of Machne, Calma and Magoun (1955) and Magoun (1958) clearly indicated an inhibitory component. In terms of cortical responsivity, the action of deepening barbiturate anaesthesia can therefore be viewed as a U-shaped curve. Concurrently with depression of the early transmission from the reticular formation there is release from inhibition in the extralemniscal system travelled by the Forbes response which therefore grows in amplitude. On increasing the anaesthetic the excitatory process too becomes depressed and eventually the cortex becomes unresponsive.

If, as it seems justifiable to propose, nonspecific ascending systems rather than the lateral pathways are involved in the sensation of pain, then one might perhaps expect some exacerbation of sensation at very light levels of induction by barbiturates. In an early study Tucci et al. (1949) found that when thiopentone was given intravenously very slowly in man, the first stage (before loss of consciousness) was marked by blurring of speech without change of respiration, eyelid tone or pupils, though with a slight but definite hyperactive response to peripheral stimulation. At this stage the e.e.g. shows only high voltage fast activity (fig. 5) and none of the slow waves usually associated with impaired consciousness, and since, in this period, there is no analgesia it is tempting to relate this fact to the finding in animals of an exaggerated cortical response to stimulation.

In connection with the suggestion of an extra-

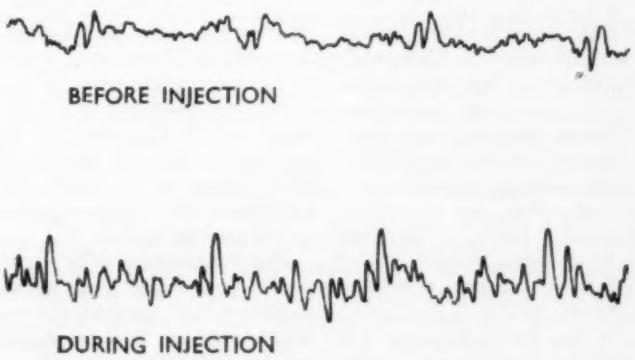


FIG. 4

Responses to flash recorded from the scalp in the occipital region of normal man during intravenous infusion (4 flashes at 1 per second flash rate).
Above: With normal saline.
Below: With dilute thiopentone.

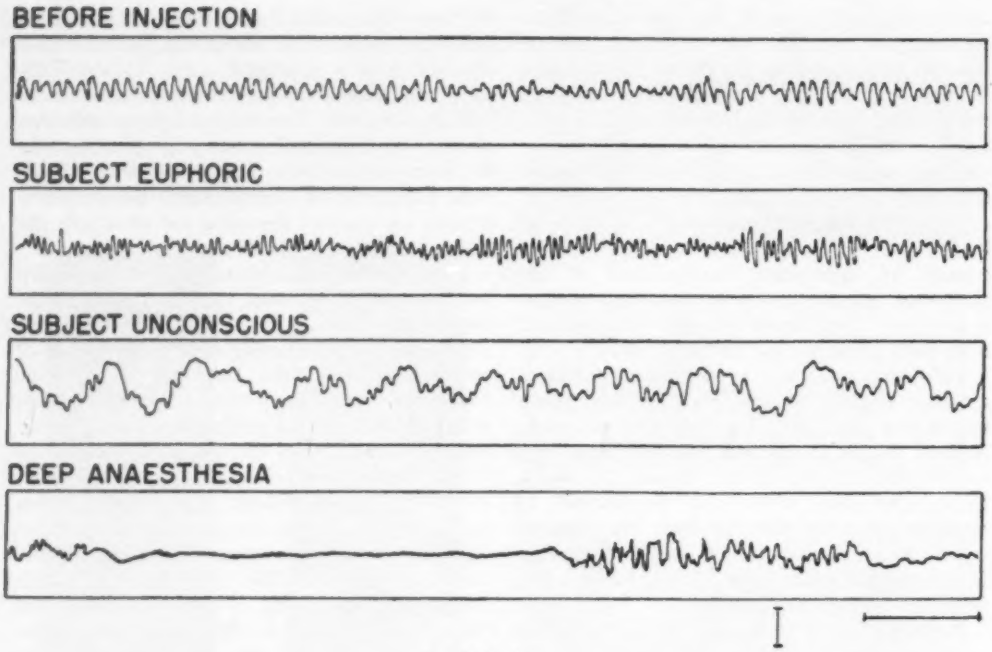


FIG. 5

Changes in the electroencephalogram of a human subject at deepening levels of thiopentone anaesthesia.
Lower right: The horizontal line represents the duration of 1 sec, the vertical line the deflection for 100 μV.
From: Brazier, M. A. B., *The Electrical Activity of the Nervous System* (2nd ed), 1960. London: Pitman. New York: Macmillan.

lemniscal route for pain, there is electrophysiological evidence from the work of Livingston, Haugen and Brookhart (1954) that stimulation of pain receptors in the tooth pulp evokes responses in the midbrain reticular substance. Responses in this region are also evoked by stimulation of the slowly conducting gamma-sized fibres of peripheral nerve which are thought to convey pain (Collins and O'Leary, 1954). Both of these effects can be abolished by anaesthesia, whether induced by barbiturates, ether or nitrous oxide (Haugen and Melzak, 1957).

The exact route of the Forbes response still remains to be charted, though it appears mainly to follow the extrathalamic branch of the ascending system from the brain stem that has been identified electrophysiologically by Starzl, Taylor and Magoun (1951a). Even less clearly understood is the vertex response found in man when consciousness is obtunded, either by natural sleep or by anaesthetic agents. This transient change in the e.e.g., named by its discoverers (Davis et al., 1938) the "K Complex", is also apparently related to the conscious state by a U-shaped curve, being absent in the waking state and in deep anaesthesia, and present only at the onset of sleep or in light narcosis (fig. 6).

The enhancement of a response by an anaesthetic agent would seem paradoxical according to concepts of some of the earlier investigators who viewed the brain as having only excitatory activity, and inhibition as being merely an absence of excitation. Modern physiology teaches us that inhibition is an active process of neurones discharging and sending impulses to impinge on other neurones, creating in them a state of hyper-

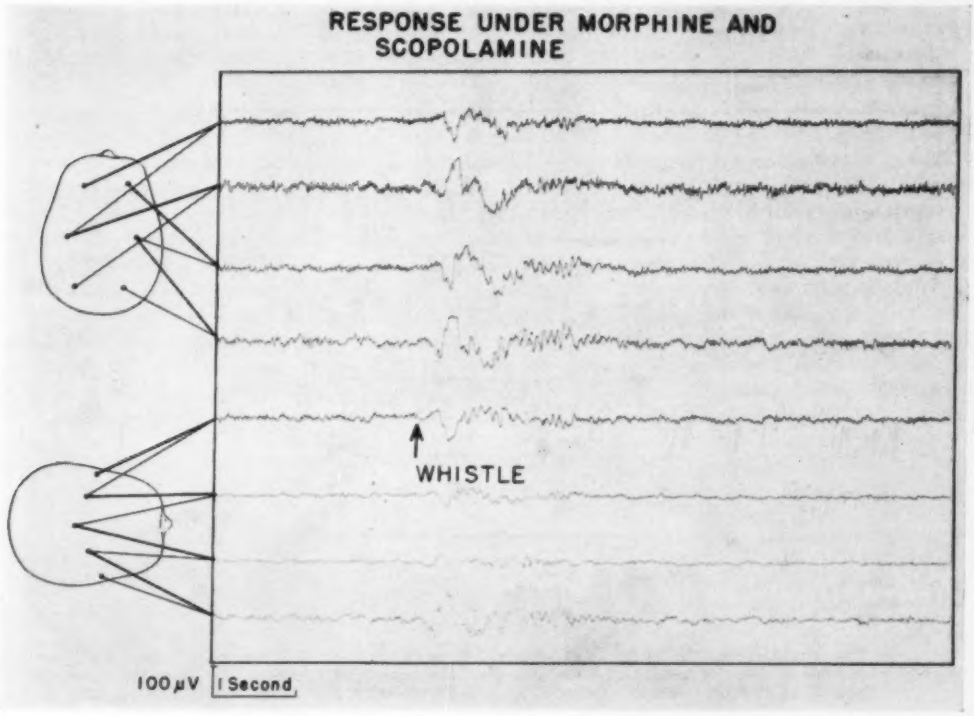


FIG. 6

The nonspecific response at the vertex of the human head, recordable only at a certain light level of anaesthesia and of normal sleep (the K-Complex).
From: Brazier, M. A. B. (1954), in *Neuropharmacology*, Abramson, H., Ed. New York: Josiah Macy Jr. Foundation.

polarization that effectively inhibits their discharge. This information about inhibition in the central nervous system was first obtained for neurones in the spinal cord (Renshaw, 1940; Eccles, 1957), but has since been demonstrated in the brain (Phillips, 1956).

Thus when some potent agent, such as an anaesthetic, reaches the brain there are two active processes upon which it can act: excitatory systems and inhibitory systems. In the unanaesthetized brain there would appear to be an effective balance between excitation and inhibition which may be regarded as part of the fine degree of homeostasis maintained in the normal state.

In the light of modern knowledge there can be little doubt that it is the ascending activating influence of the brain stem reticular system on cortical excitability that is impaired by most anaesthetics. The cortical e.e.g. signs of arousal that follow high frequency stimulation of the reticular system fail to appear in anaesthesia (Arduini and Arduini, 1954; King, 1956) (fig. 7).

The finding that anaesthetic agents prevent arousal of the cortex, not only to peripheral stimulation but also to direct reticular stimulation, would indicate that the vulnerable locus of blockade is not at the synapse where collaterals from the specific sensory pathways enter the reticular core but beyond this point (Starzl, Taylor and Magoun, 1951). In fact, at a level when the animal is anaesthetized, respon-

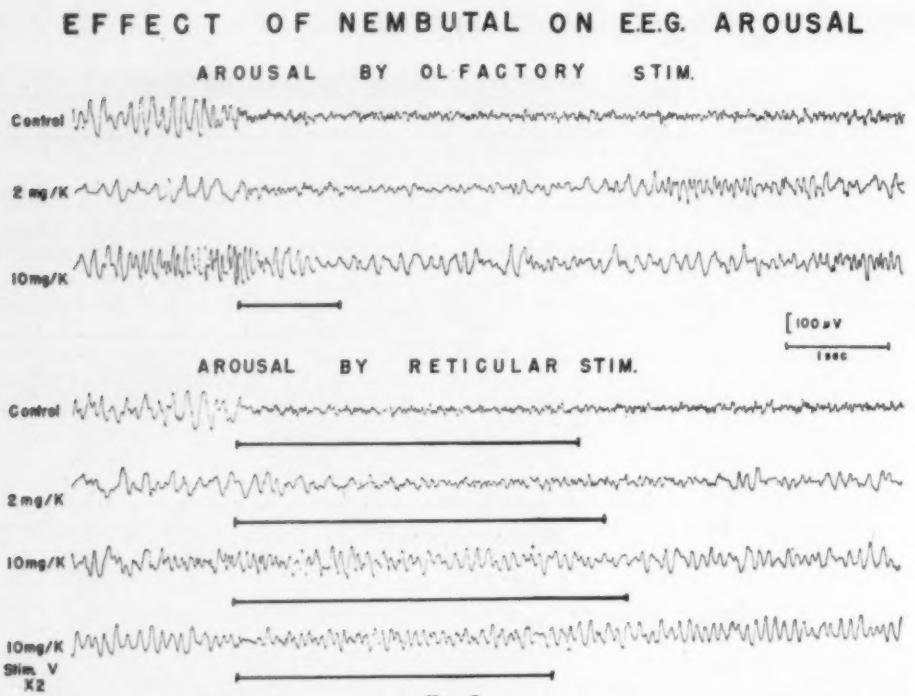


FIG. 7

The electroencephalographic arousal effect in a rabbit and the depressing effect on it of increasing doses of pentobarbitone. The black horizontal lines indicate the period of stimulation in each case. From: Arduini and Arduini (1954). *J. Pharmacol. exper. Therap.*, **110**, 76.

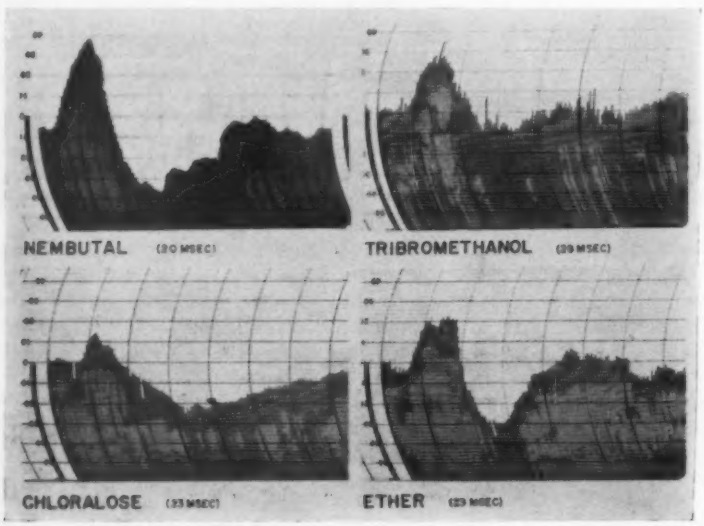


FIG. 8

Responses to flash recorded in the reticular formation in the same cat with different anaesthetic agents. Latencies to the peak of the wave are indicated. (Averages of 50 responses.)

ses to sensory stimulation can be recorded from the reticular formation (whether the agent be barbiturate, ether, chloralose or tribromethanol) (fig. 8).

At an earlier period, the ascending pathways in the reticular substance of the mesencephalic brain stem were thought to be entirely polysynaptic and to be composed only of neurones with short axons. The work of Scheibel and Scheibel (1958) on the intimate neuronal structure has more recently revealed the presence also of cells with long axons (both ascending and descending) that run almost the full length of the midbrain core. Whether or not these long fibres subserve the ascending extrathalamic route to the internal capsule, in contrast to the polysynaptic route through the midline thalamus (Starzl and Magoun, 1951; Starzl, Taylor and Magoun, 1951a, b), remains to be clarified but, if it be granted that synapses are the most probable locus of anaesthetic action (Bremer, 1937), several different sites of action are available to these drugs. The site of lowest threshold for one agent may not be the same as for another.

The polysynaptic nature of some of the components of the mesencephalic brain stem is supported by the pharmacological evidence that, at recording sites more rostral than those used for figure 8, and impairment of sensorily evoked responses by barbiturates and by ether becomes apparent (French, Verzeano and Magoun, 1953; French and King, 1955; King, 1956; Killam,

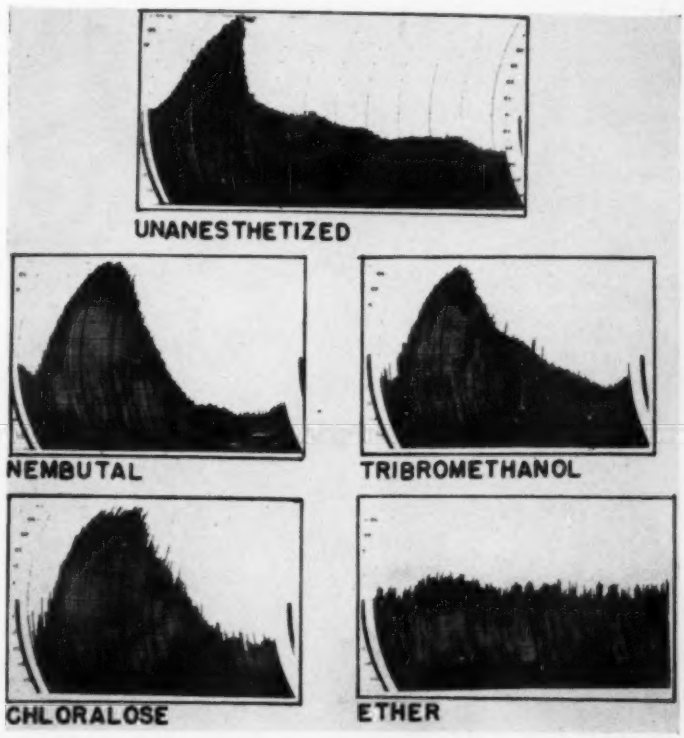


FIG. 9

Responses to flash recorded in the centre median in the same cat with different anaesthetic agents. (Averages of 50 responses.)

Killam, and Shaw, 1957; King, Naquet and Magoun, 1957). Chloralose, up to doses of about 30 mg/kg, on the contrary, does not suppress the reticular response at any level of the brain stem.

Moving up to the level of the diencephalon one finds responses in the centre median and the intralaminar cell groups of the thalamus at anaesthetic doses of barbiturates, chloralose and tribromethanol, but not with ether (fig. 9).

These nonspecific nuclei* of the thalamus and the caudate nucleus have a characteristic electrical sign by which their function can be tested. Electrical excitation by slow pulses of any one of these nuclei evokes a surface negative response on the cortex that slowly grows in amplitude during the first few pulses. This is a response, in the upper layers of the cortex, of the dendrites on to which the projections from the nonspecific thalamus make synaptic connection. This characteristic response was discovered by Dempsey and Morison (1942) and named by them the "recruiting response".

Recruiting responses, present in the awake animal (Evarts and Magoun, 1957), are abolished when it is alerted by stimulation of the reticular formation (Moruzzi and Magoun, 1949) and, conversely, become intensified with impairment of consciousness. These responses behave as

* These intralaminar groups include the following nuclei: parafasciculus, limitans, paracentralis, centralis lateralis.

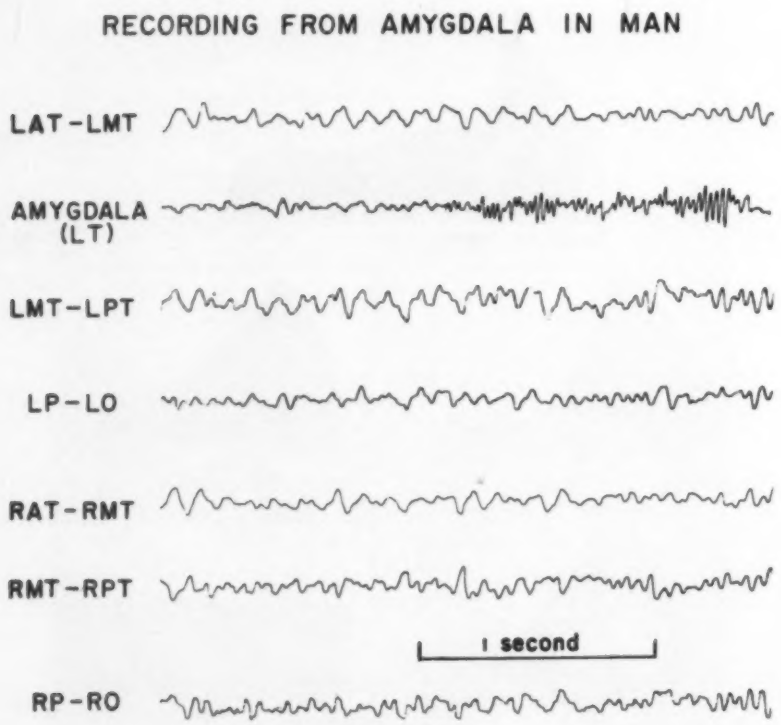


FIG. 10

An example of the fast-frequency bursts (35–40 c/s) evocable in the amygdaloid complex of unanaesthetized man during distressful episodes.

From: Brazier, M. A. B. (1960), in *Neuropharmacology*, Abramson, H., Ed. New York: Josiah Macy Jr. Foundation.

though depression of activity in the reticular formation resulted in a release of the mechanism for their production.

In studies of recruiting responses under different pharmacological conditions, King (1956) has shown them to be augmented by barbiturates and chloralose, and depressed by ether. Again the different action of ether becomes apparent. From King's experiments and from those from which figure 9 is drawn, one would conclude that ether, alone of the agents mentioned, was exerting a major depressant effect at the level of the midline thalamus.

The above review of the relative vulnerability of various sites that sensory impulses may pass through en route to the cortex has been concerned almost entirely with anaesthetic levels that more closely parallel those used in modern surgery than the heavy degree of central nervous system depression used in earlier years. When the experimental animal is taken to these deeper levels, depression of activity can be demonstrated even in the specific relay nuclei of the thalamus (King, 1956) and is especially conspicuous when the recovery cycles of these centres are tested.

Any review of this nature is bound, at present, to be a review of work in progress. Not only are the lines of research discussed here in need of further extension, but two of the questions asked in the opening paragraph are as yet almost untouched by investigators. Some anaesthetic agents used clinically suggest that their effect is essentially an impairment of storage or memory and not of sensation. Are the sites of blockade stations on the route to perception or to storage? Search for a prime focus of their action in the hippocampal regions of the brain seems worth while, and is currently being undertaken.

Is the action of some agents one on "affect" rather than on sensation ("I still feel my pain but it doesn't bother me any more")? With the recent unravelling of the role of the limbic system in the life of the emotions (MacLean, 1955a, b) some of these older rhinencephalic structures may prove to be sites of action of narcotics.

The consideration of "affect" lay, until recently, in another realm of discourse, but in recent years even this has yielded to the electrophysiologist. An electrical sign, apparently peculiar to the amygdala, has been shown (by implanted electrodes in man) to be evoked by emotionally distressing situations (Brazier, 1959) (fig. 10). The sign consists of bursts of 35 to 40 per second potentials in the amygdala which resemble rather closely those seen in animals in the stress of avoidance conditioning in which the animal must learn to escape a shock. Although the animal cannot report its distress during these episodes, as does the man, the analogy seems justifiable. This phenomenon has yet to be examined in relation to the anaesthetic state.

In the exploration of the action of anaesthetics on the central nervous system there are still many frontiers to challenge the pioneer, in addition to those mentioned in this brief review.

ACKNOWLEDGMENTS

The computer analyses in the work reported here were made possible through the co-operative programme of the Brain Research Institute at the University of California, Los Angeles, and the Center for Communication Sciences at the Massachusetts Institute of Technology.

REFERENCES

Arduini, A., and Arduini, M. G. (1954). Effect of drugs and metabolic alterations on brain stem arousal mechanism. *J. Pharmacol. exper. Therap.*, **110**, 76.

Barlow, J. S. (1957). An electronic method for detecting evoked responses of the brain and for reproducing their average waveforms. *EEG. Clin. Neurophysiol.*, **9**, 340.

Brazier, M. A. B. (1954a). A review of physiological mechanisms of the visual system in relation to activating techniques in electroencephalography *EEG Clin. Neurophysiol.*, Suppl. 4, 93.

—— (1954b). The action of anaesthetics on the nervous system. In *Brain Mechanisms and Consciousness*, p. 163. Oxford: Blackwell.

—— (1954c). Studies of the electrical activity of the brain in relation to anaesthesia. In *Neuropharmacology*, Abramson, H. Ed., p. 107. New York: Josiah Macy Jr. Foundation.

—— (1957). A study of the late response to flash in the cortex of the cat. *Acta. Physiol. Pharmacol. Neerlandica*, **6**, 692. North-Holland Publishing Co., Amsterdam.

—— (1959). In *Neuropharmacology*, Abramson, H. Ed., p. 164. New York: Josiah Macy Jr. Foundation.

—— (1960). Some actions of anesthetics on the nervous system. *Fed. Proc.*, **19**, 626.

Bremer, F. (1935). Cerveau isolé et physiologie du sommeil. *C.R. Soc. Biol. Paris.*, **118**, 1235.

—— (1937). L'activité cérébrale au cours du sommeil et de la narcose. *Bull. Acad. roy. med. Belgique.*, **2**, 68.

Collins, W. F., and O'Leary, J. L. (1954). Study of a somatic evoked response of midbrain reticular substance. *EEG Clin. Neurophysiol.*, **6**, 619.

Davis, H., Davis, P. A., Loomis, A. L., Harvey, E. N., and Hobart, G. (1938). Human brain potentials during the onset of sleep. *J. Neurophysiol.*, **1**, 24.

Dempsey, E. W., and Morison, R. S. (1942). Production of rhythmically recurrent cortical potentials after localized thalamic stimulation. *Amer. J. Physiol.*, **135**, 293.

Derbyshire, A. J., Rempel, B., Forbes, A. and Lambert, E. F. (1936). The effects of anesthetics on action potentials in the cerebral cortex of the cat. *Amer. J. Physiol.*, **116**, 577.

Eccles, J. C. (1957). *The Physiology of Nerve Cells.* Baltimore: Johns Hopkins Press.

Evarts, E. V., and Magoun, H. W. (1957). Some characteristics of cortical recruiting responses in unanesthetized cats. *Sci.*, **125**, 1147.

Feldman, S., and Porter, R. W. (1960). Long latency responses evoked in the anterior brain stem under pentobarbital anesthesia. *EEG Clin. Neurophysiol.*, **12**, 111.

Forbes, A., Battista, A. F., Chatfield, P. O., and Garcia,, J. P. (1949). Refractory phase in cerebral mechanisms. *EEG Clin. Neurophysiol.*, **1**, 141.

—— Morison, B. (1939). Cortical responses to sensory stimulation under deep barbiturate narcosis. *J. Neurophysiol.*, **25**, 112.

French, J. D., and King, E. E. (1955). Mechanisms involved in the anesthetic state. *Surgery*, **38**, 228.

—— Magoun, H. W. (1952). Effects of chronic lesions in central cephalic brain stem of monkeys. *Arch. Neurol. Psychiat.*, **68**, 591.

—— Verzeano, M., and Magoun, H. W. (1953). A neural basis of the anesthetic state. *Arch. Neurol. Psychiat.*, **69**, 519.

Haugen, F. P., and Melzak, R. (1957). The effects of nitrous oxide on responses evoked in the brain stem by tooth stimulation. *Anesthesiology*, **18**, 183.

Killam, E. K., Killam, K. F., and Shaw, T. (1957). The effects of psychotherapeutic compounds on central afferent and limbic pathways. *Ann. N.Y. Acad. Sci.* **66**, 784.

King, E. E. (1956). Differential action of anaesthetics and interneuron depressants upon EEG arousal and recruitment responses. *J. Pharmacol. exper. Therap.*, **116**, 404.

—— Naquet, R., and Magoun, H. W. (1957). Alterations in somatic afferent transmission through the thalamus by central mechanisms and barbiturates. *J. Pharmacol. exper. Therap.*, **119**, 48.

Lindsley, D. B., Schreiner, L. H., Knowles, W. B., and Magoun, H. W. (1950). Behavioral and EEG changes following chronic brain stem lesions in the cat. *EEG Clin. Neurophysiol.*, **2**, 483.

Livingston, W. K., Haugen, F. P., and Brookhart, J. M. (1954). The vertical organization of function in the central nervous system. *Neurol.*, **4**, 485.

Machne, X., Calma, L., and Magoun, H. W. (1955). Unit activity of central cephalic brain stem in EEG arousal. *J. Neurophysiol.*, **18**, 547.

MacLean, P. D. (1955a). The limbic system ("visceral brain") and emotional behavior. *Arch. Neurol. Psychiat.*, **73**, 130.

—— (1955b). The limbic system ("visceral brain") in relation to central gray and reticulum of the brain stem; evidence of interdependence in emotional processes. *Psychosom. Med.*, **17**, 547.

Magoun, H. W. (1958). *The Waking Brain.* Springfield: Thomas.

Moruzzi, G., and Magoun, H. W. (1949). Brain stem reticular formation and activation of the EEG. *EEG Clin. Neurophysiol.*, **1**, 455.

Phillips, C. G. (1956). Intracellular records from Betz cells in the cat. *Quart. J. Physiol.*, **41**, 58.

Purpura, D. P. (1955). Further analysis of evoked "sensory discharge"; a study in reticulo-cortical relations. *J. Neurophysiol.*, **18**, 246.

Renshaw, B. (1940). Observations on interaction of nerve impulses in the grey matter and on the nature of central inhibition. *Amer. J. Physiol.*, **146**, 74.

Scheibel, A. B., and Scheibel, M. E. (1958). Substrates for integrative mechanisms in the brain stem reticular core. In *Reticular Formation.* Boston: Little, Brown.

Starzl, T. W., and Magoun, H. W. (1951). Organization of the diffuse thalamic projection system. *J. Neurophysiol.*, **14**, 133.

—— Taylor, C. W., and Magoun, H. W. (1951a). Ascending conduction in reticular activating system with special reference to the diencephalon. *J. Neurophysiol.*, **14**, 461.

—— —— —— (1951b). Collateral afferent excitation of reticular formation of brain stem. *J. Neurophysiol.*, **14**, 479.

—— Whitlock, D. G. (1952). Diffuse thalamic projection system in monkey. *J. Neurophysiol.*, **15**, 449.

Tucci, J. H., Brazier, M. A. B., Miles, H. W., and Finesinger, J. E. (1949). A study of pentothal sodium anesthesia and a critical investigation of the use of succinate as an antidote. *Anesthesiology*, **10**, 25.

Brit. J. Anaesth. (1961), **33**, 205

ELECTROENCEPHALOGRAPHY

BY

JOHN CLUTTON-BROCK
Department of Anaesthetics, University of Bristol, England

DURING normal life the brain is in a state of constant electrical activity. Electrical activity, though in a modified form, continues throughout deep sleep and coma but can be stopped reversibly by temporary lack of oxygen or deep anaesthesia. This electrical activity was first demonstrated by a Liverpool physician, Richard Caton, who connected a sensitive galvanometer to the exposed cerebral cortex of animals. An account of his experiments was described in the *British Medical Journal* of 1875 (Caton, 1875). It was not, however, until 1928 that these electrical currents were recorded from the outside of a human skull (Berger, 1929). At this time Berger, using a simple adaptation of an electrocardiograph, made the first recording of a human "elektrenkephalogramm" as he named it. For his early experiments he inserted silver wires under the subject's scalp. These wires were connected to an Edelmann galvanometer and the records were photographed. The smallest electrical activity Berger was able to detect was about 100 μV. With this degree of sensitivity the record just showed a slight wobble at about 10 c/s. Berger was able to show that this rhythm tended to stop when the subject opened his eyes or did mental arithmetic. Berger made his connection from the front and the back of the head, and supposed that this electrical activity, at about 10 c/s, came from the whole of the brain; and it was not until considerably later that Adrian and Matthews showed that this rhythm arises in the visual association areas of the occipital cortex (Adrian and Matthews, 1934). The maximum sensitivity of present-day apparatus is usually such that a signal of 10 μV will produce a deflection of 1 cm on the recording device. This sensitivity is about 100 times greater than that of the apparatus used by Berger.

Before going further into the matter some consideration of the apparatus is necessary. Perhaps it is as well at the outset to say that the apparatus is the electroencephalo*graph*, and that the record from the apparatus is the electroencephalo*gram*. Any confusion is usually avoided by calling them both indiscriminately the e.e.g. Fundamentally, what the instrument has to do is to amplify the minute signals from the brain of the subject until they will produce on the recording device a deflection of a suitable size. This may involve an amplification of some four million times. Since a modern amplifying valve will magnify the voltage more than 100 times, it would seem that three stages of amplification, each consisting of a single valve, would do all that is necessary. Unfortunately, the problem is, in practice, greatly complicated by the presence of stray voltages of varying sorts which are very large in comparison with the voltages it is desired to record. Any electrical conductor, including the human body, will pick up a large amount of electricity from any apparatus or wires anywhere near it. These interference voltages from the mains supply at 50 c/s can be very large indeed and it is almost impossible entirely to screen the subject from them. If the subject's head were connected to three simple stages of amplification and this to a suitable inkwriter, the pen of the inkwriter would just vibrate all over the paper at 50 c/s, splashing those around with ink, and no e.e.g. signal would appear. There are other sources of interference as well as those coming from the electricity supply. For example, the voltages generated by the heart are much greater than those recorded during electroencephalography, and these e.c.g. voltages may appear on the record; however, the alternating electrical supply causes by far the greatest amount of trouble. During the early days of electroencephalography, the subject was often put into a metal cage and chained to this by his leg; this was not to prevent his escape

but to reduce electrical interference. Nowadays this sort of screening is not necessary though it is as well to avoid putting any electrical apparatus or wires too close to the subject. Modern e.e.g. amplifiers are designed to reject the unwanted interference signals and to record only those which are required. The general principle behind this sorting out of interference is that the voltages generated by interference are in the same direction at each electrode, but those required are in opposite directions, i.e. the amplifier is designed so as to take notice only of the differences in voltages between the two leads coming from the subject's scalp and to disregard the voltages occurring equally in the two leads. Interference can further be reduced by earthing the patient through some suitably placed electrode. In this way the e.e.g. amplifier can record a wanted signal which is only of the order of 1/1000th the size of the interfering signal. After the signals have been sorted out and amplified, they may be recorded on paper by an inkwriter. The paper speed is usually 1½, 3 or 6 cm/sec, depending on the circumstances. It is sometimes suggested that it may be quite sufficient, for anaesthetic purposes, to monitor the e.e.g. on a cathode ray oscilloscope, but it is always advisable to have an inkwriter as well so that a permanent record may be made of any changes. Without this record adequate examination and comparison is impossible. In most instruments a number of separate channels of amplification, each with its own inkwriter, is usually available. This may be anything from 2 to 16 or more, depending on the purposes to which the apparatus is to be put.

Connection, of course, has to be made to the patient's scalp: and in the conscious subject this is usually by means of electrodes either strapped or stuck on to the surface. Surface electrodes must be contrived so that they are non-polarizing, i.e. that the resistance does not alter with a flow of electricity: and for this purpose small pieces of silver are used, and the area which is to be in contact with the patient's scalp is covered electrolytically with a thin film of silver chloride. When the minute currents to be recorded pass through these electrodes they either add to, or reduce slightly, the layer of silver chloride. This does not significantly alter the electrical resistance of the system. The electrical resistance would alter considerably if plain silver were used because on one electrode there would be a deposit of silver chloride, and on the other a small amount of hydrogen would be liberated. Before the silver chloride electrodes are applied, grease must be removed from the scalp with spirit. Contact is made between the scalp and the electrode by means either of small pads soaked in saline or a small quantity of electrode jelly such as is used for electrocardiography. When the subject is unconscious, as for example, during anaesthesia, stainless steel hypodermic needles may be pushed into the scalp and these make excellent electrodes, although the permanent film of oxide prevents direct electrical contact.

For standard electroencephalography there are recognized places for the electrodes, but they may be placed elsewhere on the scalp for a particular purpose. The first thing that must be made clear about the output of the brain seen in an e.e.g. in normal subjects is that it may be largely rhythmical or largely desynchronized. "Rhythmical" means that there is a repetitive signal at a certain frequency. For a rhythm to be detectable in the e.e.g. at least one million cells of the brain must be beating in unison. The frequency of the rhythm is more important than the amplitude and it is usual to divide the rhythms into various frequency bands. Rhythms from ½ to 3½ c/s are termed "delta" rhythms; from 4 to 7 c/s are "theta" rhythms; from 8 to 13 are "alpha"; those having a frequency higher than this, from 14 to 30 c/s are "beta"; rhythms having a frequency higher than 30 c/s are occasionally encountered but are of little interest to the anaesthetist.

As previously stated, Berger (1929) noticed a rhythm in his original e.e.g. at about 10 c/s. This he called the alpha rhythm because it was the first to be discovered. In the majority of people the alpha rhythm tends to disappear when the eyes are opened—or when the subject does mental arithmetic—and reappears when his eyes are shut (fig. 1). The alpha rhythm is seldom at one single frequency, but is usually compound at various frequencies about 10 c/s. It is thus associated with inactivity of the visual cortex rather than with activity. The alpha rhythm may represent a scanning mechanism; i.e. the brain is seeking for something to look at, and when it

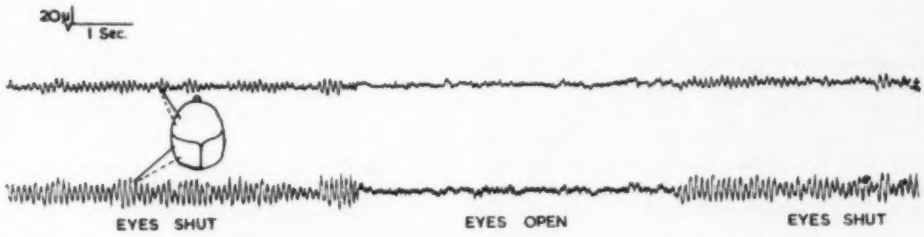


FIG. 1
Alpha rhythm showing the effect of opening the eyes.

finds this the scanning mechanism stops. This responsive type of alpha rhythm occurs in about two-thirds of the population. In approximately one-sixth of the population the alpha rhythm is present all the time, whether the subject has his eyes open or not, and in the remaining one-sixth the alpha rhythm tends to be absent even when the eyes are closed.

Walter and his co-workers have shown that these differences in the alpha rhythm can be related to personality differences (Walter, 1953). The subject who has a persistent alpha rhythm tends to solve all his problems in a theoretical fashion; the person without an alpha rhythm, in a visual manner. When the latter shuts his eyes he continues to see, as it were, in his mind's eye. The subject with a persistent alpha will see just as clearly as the subject without an alpha rhythm; but he has not the same power of visualization. Some recent experiments by Walter and his co-workers (Walter, 1959), using lysergic acid diethylamide which tends to give hallucinations, have shown that hallucinations can be produced most readily in those people who have a persistent alpha rhythm; this tends to be suppressed when the hallucinations occur. If, however, the drug is given to a subject without an alpha rhythm, although he feels estranged from his surroundings, hallucinations are not produced. It would seem that the hallucinations of the subject with a persistent alpha rhythm are normally experienced by the subject without an alpha rhythm, and are no more than the habitual vivid picture in his mind's eye.

In young children slow rhythms are normal but an alpha rhythm begins to make its appearance at about 3–4 years of age, though it can be detected in some children younger than this. Before the age of 3–4 any alpha rhythm present is usually unresponsive to visual stimuli and only begins to show a connection with vision at this age. The classical blocking reactions appear clearly in some children at 6–7 years but the adult pattern is not found fully developed before the age of 10–11 (Walter, 1953). To say that in children the alpha rhythm has a frequency of 4–8 c/s (Faulconer and Bickford, 1960) is misleading and overlooks the development and mechanics of this important sign of cerebral function.

"Delta" rhythms, i.e. those having a frequency of between $\frac{1}{2}$ to $3\frac{1}{2}$ c/s, tend to arise in the prefrontal areas, and were called delta rhythms because of their apparent association with disease, degeneration and death, but they may be not so much a sign of degeneration as a sign of defence against it. They occur naturally in very young children, and are thus associated with development. They also occur during sleep and with deep respiration, or more strictly speaking, overventilation. Delta rhythms are often produced by hypoxia which, of course, leads to degeneration. These various situations, all beginning with "d", may help to remind the reader of conditions with which a delta rhythm is usually associated. The slow waves in the delta range tend to have a very large amplitude; and Walter (1953), considers that the defence mechanism involved, if indeed this is what it is, may consist of a slow short-circuiting of all other activity of the cortex. During infancy the slow waves may prevent uncontrolled activity that might be harmful. It may be that during sleep the delta waves keep the subject asleep. He is rocked to sleep,

as it were, by his own cortical rhythms. There is one particular type of slow wave occurring during sleep that seems to confirm the above suggestion. This is the "K complex", described by Davie et al. (1939). This wave spreads all over the cortex and is produced by a stimulus which would otherwise tend to awaken the subject. Figure 6 on page 199 shows the occurrence of such a "K complex", produced on this occasion by a loud sound. It must be stressed that the "K complex" is only produced when the subject fails to be awakened by the stimulus.

During overventilation it might be that alkalosis would lead to an increased irritability of the cortex which is short-circuited in the manner described; for example, in certain subjects overventilation can give rise to epileptic attacks. There is no constancy in the delta rhythm's association with overventilation: in some people it occurs readily, in others not at all. It is in no way a sign of the degree of cerebral upset produced. The most that can be stated is that the younger the subject the more readily does it occur. In the case of a disease—perhaps a cerebral tumour—producing a delta rhythm, it might be that this would cause some harmful electrical activity if the delta rhythm were not present. Deep anaesthesia with many agents will produce slow waves on the e.e.g. Hypoxia will often result in slow waves before the typical flattening of the e.e.g. occurs. The slow wave response, therefore, is far from specific!

The theta rhythms, so called because it is thought that they have their origin in the thalamus, are particularly common and widespread in children; they seem to be largely associated with the emotional outbursts to which small children are so prone. It has been shown that feelings of frustration and irritation in adults may also produce a theta rhythm; and when this is particularly easily provoked it may be that this person, like a child, lacks the tranquillity and emotional control which usually comes with adult life.

The more rapid rhythms, the beta rhythms, which tend to arise in the pre-frontal region, can be produced by considerable excitement on the part of the subject, and are associated with certain levels of anaesthesia with certain agents. Artusio

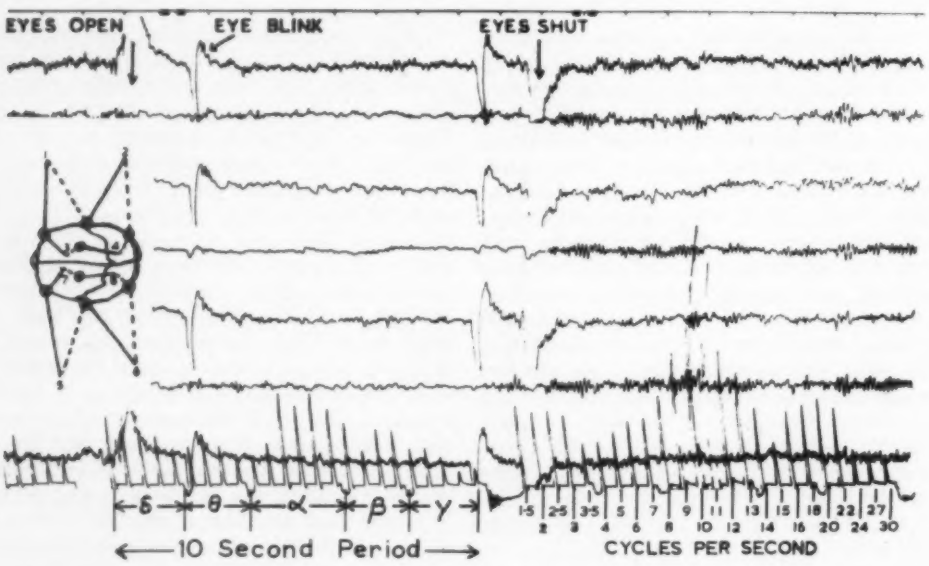


FIG. 2

Automatic frequency analysis of e.e.g. (see text). The two dark squares on the top line show that it is channel two that is being analyzed.

has described a beta rhythm at about 24 c/s accompanying the stage of analgesia with ether (Artusio, 1955). The author has seen—on a few occasions—a beta rhythm accompanying light anaesthesia with nitrous oxide and oxygen, though this is unusual. An e.e.g. may contain rhythms at many frequencies which it may not be possible to recognize by eye. To investigate the rhythmic contents of these records a frequency analyzer was developed by Walter and Baldock (1946). This displays the amplitude of each component as a separate trace. To perform this analysis the output from any desired channel in the e.e.g. is scanned over a 10-second period by a series of electrical resonators. The bottom of figure 2 shows such an automatic analysis superimposed on the ordinary e.e.g. record. The height of each trace corresponds to the proportion of the signal at each frequency in the channel under investigation. Other methods of frequency analysis are also in use.

The effect of various anaesthetic agents on the e.e.g. in man and animals has been very fully described in the literature, and is well summarized by Faulconer and Bickford (1960). Without going into details of the individual effects of various agents, deepening anaesthesia in general is associated first with the replacement of the alpha waves by high frequency activity within the beta range arising in the first place from the prefrontal regions. This may be of high or low voltage, depending on the agent used. This high frequency activity is then replaced by high voltage slow waves. With some agents, e.g. ether and thiopentone, further deepening of anaesthesia is characterized by this slow activity becoming intermittent with increasingly long periods of electrical silence between bursts of activity, the so-called burst suppression. With nitrous oxide, however, the effects are variable, and are modified by premedication with opiates (Henrie et al., 1960). Often, however, the only effect of nitrous oxide and oxygen anaesthesia in clinical practice is to cause a previously responsive alpha rhythm to become unresponsive. The author has seen complete analgesia with a responsive alpha rhythm, and a responsive alpha rhythm in one subject who appeared to be unconscious.

Nitrous oxide with adequate oxygen seems, therefore, to produce unconsciousness with the least change in the e.e.g.: whether this is an indication for its use is debatable, but it would certainly suggest that its effect is confined to the reticular system, which may be desirable in an anaesthetic agent. Interference with cerebral blood flow produces obvious changes rapidly. The first major change after a transient increase in the high frequency components is usually the appearance of large amplitude slow waves which may progress to electrical silence if the interference with blood supply is severe and prolonged (fig. 3). These changes are probably due to cerebral hypoxia though this may not be the only factor (Pampiglione, 1960). This early sensitive indication of cerebral hypoxia is perhaps the most important indication for electroencephalography during anaesthesia, though it is not easy to relate the duration of severe hypoxic signs to the ultimate survival of the patient. A patient may recover rapidly and completely after half an hour with a completely flat e.e.g., though if this persists for some hours there is little chance of survival (ibid.). It seems possible that a period of hypoxia may make the brain more sensitive to anaesthetic agents after the hypoxia has been relieved (Clutton-Brock, 1959).

Since the introduction of electroencephalo-

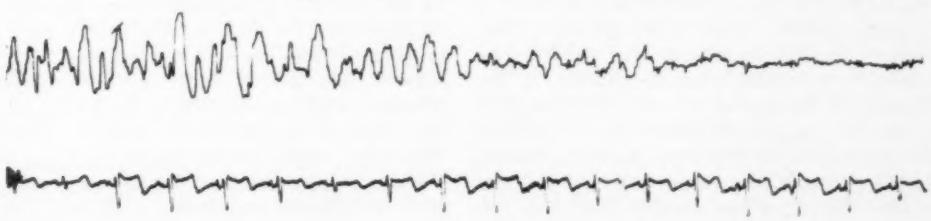


FIG. 3

Effect of cerebral hypoxia. Top line e.e.g. Bottom line e.c.g.

graphy other methods of investigating the activity of the brain have been developed. Some of the most important of these have led to experiments into the response by the brain to sensory stimuli. There are two pathways by which sensory stimuli can reach the cerebral cortex. Through the first of these, the lemniscal path, the sensory stimulus causes a response at the primary reception area. Sensory stimuli may also travel, however, to the cortex via the reticular system in the brain stem and cause a secondary response in the association areas. The primary pathway is but little affected except by deep anaesthesia, and it would seem that anaesthetists are mainly concerned with the effects of their anaesthetic agents on the secondary responses. The pathway for these secondary responses from the reticular system in the brain stem to the cortex has been called the nonspecific cortical projection system and is very sensitive to anaesthetic agents. Until recently it was only to one form of sensory stimulus that the responses could be detected by electrodes on the scalp. This is an intense and very brief flash of light. In many people the bright flashes produce responses which can be recorded with suitable equipment from large areas of the cerebral cortex. Bright flashes of light—so bright that it is immaterial whether the subject has his eyes shut or open—are usually applied in rhythmic fashion, often at or about the frequency of the alpha rhythm. This flashing light is conveniently known as "flicker". So powerful a stimulus is this that at the right frequency and in a susceptible subject, an epileptic attack can be produced. A conventional e.e.g. is unfortunately unsuitable for investigation into the responses to flicker, because one cannot be sure whether any rhythm that one sees on the paper is at exactly the same frequency as that of the stimulus, which it would be if it were caused by the stimulus. A frequency analyzer as previously described may be used in association with an e.e.g. to determine whether a dominant rhythm appears at the frequency of the applied stimulus. However, it is possible, in some people, for the stimulus to alter the frequency of the subject's own alpha rhythm to make this coincide with the stimulus; so that for any satisfactory investigation into these responses some rather more elaborate apparatus is necessary. For this purpose the Grey Walter toposcope (Walter and Shipton, 1957) has shown itself to be ideal.

This apparatus consists of 22 separate amplifier channels, each connected to separate electrodes on the subject's scalp. The output of each of these channels of amplification is displayed on a separate small cathode ray tube. These cathode ray tubes are arranged with the same spatial orientation as the electrodes on the subject's scalp. There is a further cathode ray tube which monitors the flicker. The output from each amplifier is arranged so as to alter the brightness of the spot on the cathode ray tube. In each tube the spot is caused to move from the centre of the tube outwards in a helical (spiral) fashion. When the spot arrives near the periphery of the tube it is made to move rapidly back to the centre, and the scan begins again. Each scan takes about 8 seconds. The rotational speed of this helical scan can be synchronized either to the flicker or to any inherent rhythm which may be present, and which it is desired to investigate. The whole display may be photographed automatically. Figure 4 shows the response to flicker in a normal subject. The small cathode ray tube at the top centre of the picture shows as a time-relationship the flashes of light that form the stimulus. These flashes appear as radial arms on the tube. If there is a response to this stimulus, then a radial arm of light will appear on the cathode ray tube corresponding to the position on the subject's head where the response appeared. If there is a rhythm unrelated to the stimulus then it will appear as a helical and not as a radial arm. By comparing the position of these radial arms of light on the various cathode ray tubes with the radial arms on the cathode ray tube monitoring the flashes of light directly, not only may the presence of a response be determined, but also the time relationship of this response to the stimulus. This time relationship is a measure of the time delay between the stimulus and the response. As stated earlier on, the rhythmic stimulus may cause an alpha rhythm to synchronize with the stimulus, and thus an inherent rhythm may appear to be a response to a stimulus. However, if the stimulus is applied so as to form some recognizable pattern, e.g. every fourth flash may be omitted, then the true response will follow the pattern of the stimulus; whereas if the inherent

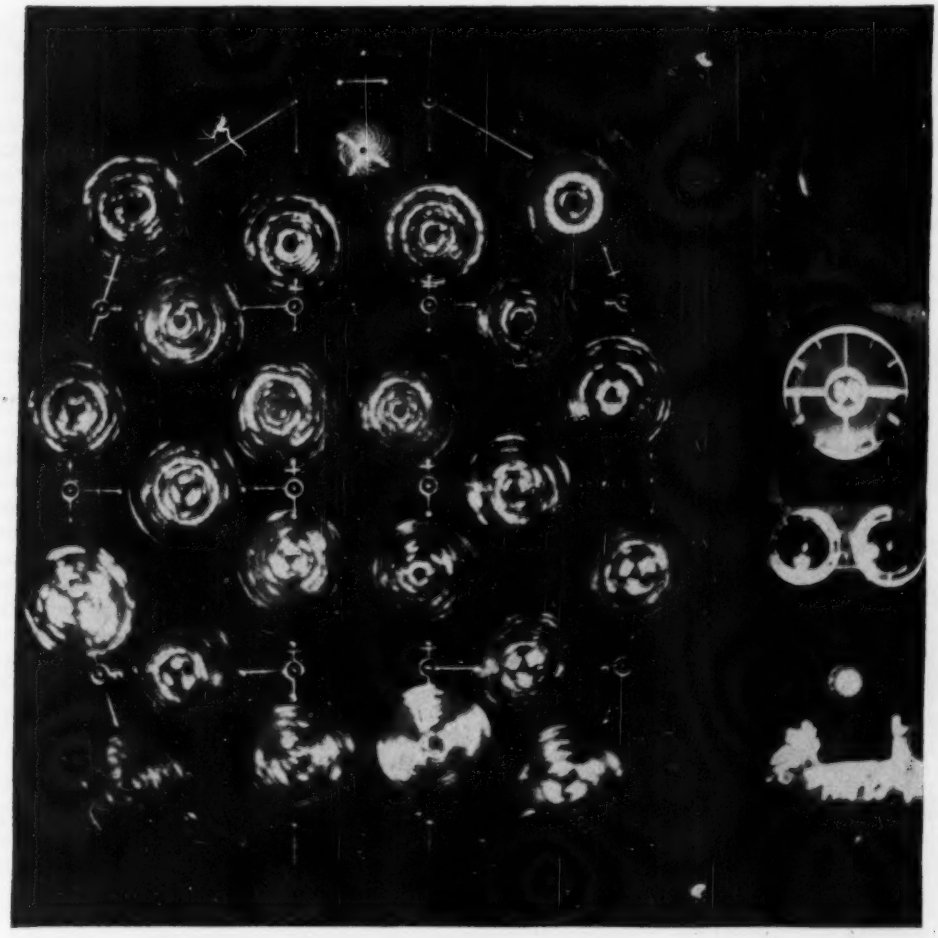


FIG. 4

Toposcopic response to flicker (see text). The cathode ray tubes at the bottom right of the picture shows a clear response.

rhythm has merely been synchronized to the stimulus, the pattern will not appear. This apparatus has been used to investigate the effects on the nonspecific projection system, of drugs, the formation of conditioned reflexes, learning, and for a great many other experiments. It is impossible to take the apparatus in its present form into the operating theatre to investigate the effects of anaesthesia, but so far one experiment has been made on a volunteer using anaesthesia with nitrous oxygen and oxygen and full paralysis provided by gallamine (Walter and Clutton-Brock, 1957). This experiment showed that the area of the cortex where responses occurred grew smaller and smaller as anaesthesia deepened, rather like the tide retreating from the seashore, until finally no response was left. No effect from full relaxant doses of gallamine could be detected. The toposcope may also be used to investigate the distribution of alpha rhythms and other functions.

Clutton-Brock (1961) has designed a modification of the Grey Walter toposcope for single-channel use. This can be taken into the operating theatre. The apparatus is largely made up of equipment to be found in any research laboratory. As in the Grey Walter toposcope, the output from the e.e.g. modulates the brightness of the beam in a cathode ray tube, but a rectangular scan is used instead of a helical one. The display is very like that used on a television set except that it is much slower, and takes 10 seconds. Figure 5 shows a response to flicker in a normal subject. On the upper part of the cathode ray tube the downward deflections are caused directly through an amplifier by the flashes of light. The response to flicker appears below this scan as a series of light and dark bands. If any rhythm present is related to the stimulus, these bands will be vertical: if unrelated, they will be at an angle. A pattern of flicker can also be used with this apparatus. Figure 6 shows the effect of an increasing concentration of nitrous oxide on a volunteer. The lefthand display shows an obvious response to the stimulus, the centre display shows the response still just there, and the righthand display shows that there is no response but that there is a rhythm present unrelated to the stimulus. Experiments with this apparatus suggest that in the case of nitrous oxide and oxygen, absence of a previously present response to flicker indicates unconsciousness, though where thiopentone is used, the response to flicker disappears before consciousness is lost. Until recently, it was almost impossible in man, without operative interference, to investigate the responses to any stimulus other than flicker. This was because the potentials reaching the outside of the scalp in response to other stimuli were so minute in relation to inherent rhythms in the brain and other sources of interference. Recently a method of averaging out the interfering signals and summating the desired signals has been developed using a barrier grid storage tube (Buller and Styles, 1959). With this, it is possible that the responses to all sorts of modalities of sensation may be recorded, and experiments in these directions are in progress in many centres.

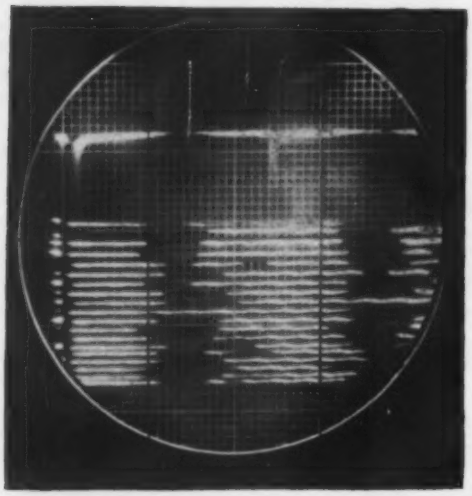


FIG. 5
Response to flicker (see text).

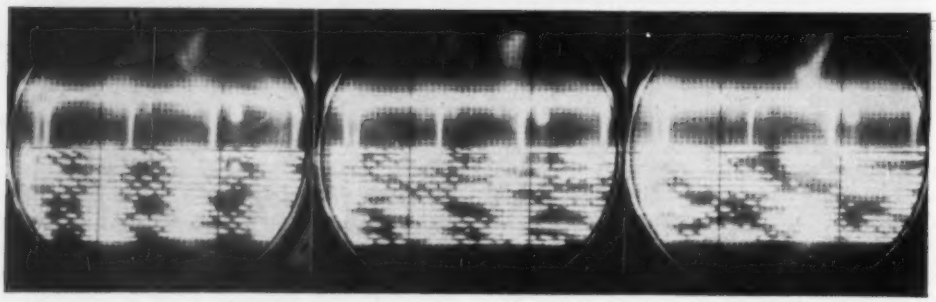


FIG. 6
Effect of N_2O on flicker response (see text).

SUMMARY

The various rhythms recordable on the e.e.g. can often be related to various states of activity (or otherwise) of the cerebral cortex, but it is often impossible to relate the presence or absence of the various rhythms with consciousness or unconsciousness, unless something else is known about the state of the subject, e.g. the presence of a delta rhythm does not mean that the subject is unconscious. This can be produced by overventilation, with the subject remaining normally in possession of his faculties. If however, it is known that the subject is asleep, then how deeply asleep he is, is apparent from the e.e.g. With certain anaesthetic agents some information can be gained from the e.e.g. as to how deeply asleep the patient is, but this may not always be completely reliable in man (Saltero, 1951; and Brand, 1960). With nitrous oxide and oxygen, anaesthesia may be associated with well-marked changes, but it can also occur, in certain people, with little or no change at all. It seems, therefore, that information about the state of consciousness or otherwise of a patient lightly anaesthetized and fully paralyzed may be obtained by investigating the secondary responses to stimuli travelling via the nonspecific projection system.

ACKNOWLEDGMENTS

It gives me the greatest pleasure to acknowledge my indebtedness to Dr. W. Grey Walter and to Dr. R. Cooper, both of the Burden Neurological Institute, Bristol, for their help in preparing this brief introduction to electroencephalography.

REFERENCES

Adrian, E. D., and Matthews, B. H. C. (1934). The Berger rhythm; potential changes from the occipital lobes in man. *Brain*, **57**, 355.

Artusio, J. F. jnr. (1955). Ether analgesia during major surgery. *J. Amer. med. Ass.*, **157**, 33.

Berger, H. (1929). Unber das Elektrenkephalogramm des Menschen. *Arch. Psychiat.*, **87**, 527.

Brazier, M. A. B. (1961). Some effects of anaesthesia on the brain. *Brit. J. Anaesth.*, **33**, 194.

Buller, A. J., and Styles, P. R. (1959). A new averaging technique for improving signal to noise ratio of evoked potentials. *J. Physiol.*, **149**, 65 P.

Caton, R. (1875). The electric currents of the brain. *Brit. med. J.*, **2**, 278.

Clutton-Brock, J. (1961). A new electroencephalographic display. *Proc. 3rd International Conference on Medical Electronics* (in publication).

Davie, H., Davis, P. A., Loomis, A. L., Harvey, E. N., and Hobart, G. A. (1939). Electrical reactions of human brain to auditory stimulation during sleep. *J. Neurophysiol*, **2**, 500.

Faulconer, A. jnr., and Bickford, R. G. (1960). *Electroencephalography in Anesthesiology*, Ed., p. 8. U.S.A.: Thomas.

Henrie, Joyce, R., Parkhouse, J., and Bickford, R. G. (Unpublished data quoted in the above.)

Pampiglione, G. (1960). Neurophysiological aspects of cerebral ischaemia. *Proc. roy. Soc. Med.*, **53**, 329.

Walter, W. Grey (1953). *The Living Brain*, p. 148. London: Duckworth.

—— (Personal communication.)

—— Baldock, G. R. (1946). A new electronic analyzer. *Elec. Engineering*, **18**, 339.

—— Shipton, H. N. (1957). The brain as a machine. *Proc. roy. Soc. Med.*, **50**, 799.

—— Clutton-Brock, J. (1957). (Unpublished observation quoted in *Modern Trends in Anaesthesia*. T. Frankis Evans and T. C. Gray, 1958). London: Butterworth.

Brit. J. Anaesth. (1961), 33, 214

THE IMPORTANCE OF THE CENTRAL NERVOUS EFFECTS OF ANAESTHETIC AGENTS

BY

J. CLUTTON-BROCK
University of Bristol, England

GENERAL anaesthesia produced by various agents has been used to prevent the pain of surgical operations for a little over a hundred years, but it is only very recently that some understanding has been reached of the mode of action of these agents on the central nervous system. Before the days of relaxant drugs very much larger doses of anaesthetic agents were given than those just necessary to produce unconsciousness, so it is perhaps not surprising that the effects of these anaesthetic agents on other systems in the body, such as the cardiovascular and respiratory systems, were of more importance to the anaesthetist than the effects on the sensory portion of the central nervous system. With deep anaesthesia the patient is certainly unconscious and, if he dies, this is not due to the effect of the anaesthetic agent on the sensorium but usually to the effect of overdose or hypoxia on the cardiovascular or respiratory systems. Now, however, that all the muscular relaxation and immobility necessary for major surgery can be produced by drugs that in normal doses have little if any central nervous effect, the general anaesthetic agent is given in doses sufficient only to produce such central nervous depression as the anaesthetist thinks is suitable.

With the growth of knowledge of the working of the central nervous system, insight has come into the mode of action of anaesthetic agents, and this is of more than academic interest to the working anaesthetist; if the general anaesthetic agent is to be given in doses sufficient only to produce such central nervous depression as the anaesthetist thinks is right, some important problems arise, two will be considered here. First, what is the optimum depth of anaesthesia to be used when the patient is fully paralyzed with the relaxant drug? Second, how can it be decided that the patient is in this optimum plane of anaesthesia? Opinion is much divided among anaesthetists on the first problem. Artusio (1955) uses analgesia only—produced by ether—for cardiac surgery. With his technique the patient is free from pain but is able to answer simple questions by means of signals. Loder (1957), however, considers that nervous stimuli during very light anaesthesia may be harmful. Moreover, there is always the danger that a paralyzed patient may be conscious and in pain during an operation, and unable to make his unpleasant state known to the anaesthetist. In order both to avoid the danger of the patient being conscious during the operation and the possibility of harmful effects of nocciceptive stimuli, many anaesthetists give anaesthesia somewhat deeper than that necessary just to produce unconsciousness. Others feel that the minimum dose should be given because anaesthetic agents are generalized poisons. For example, the induction dose of an intravenous barbiturate given by one anaesthetist may be at least five times that given by another, for the same type of patients. One anaesthetist may supplement anaesthesia provided by nitrous oxide and oxygen with regular doses of pethidine or some other narcotic; or he may hyperventilate the patient knowing that this causes some analgesia in the conscious subject (Clutton-Brock, 1957; Editorial, 1880), probably by depression of the reticular system which is very sensitive to the carbon dioxide tension in the arterial blood; others feel that these manoeuvres are unnecessary.

While it is as yet impossible to give any definite answer to either of the two problems, recent neurophysiological research suggests that the answers may soon be forthcoming; meanwhile it behoves anaesthetists to know how far neurophysiologists can answer these problems quite apart from the academic interest of knowing how anaesthetic agents work.

Theoretical optimum depth of anaesthesia.

It can probably be agreed that the patient should be perfectly comfortable and must not be sufficiently aware of his surroundings to be frightened or upset by them. This upset may be caused by his overhearing what the surgeon has to say—for example, "Let's sew the old bag up now"—or by feeling the surgeon at work in his abdomen, even if there is no pain. Anaesthetists may think it is better that the patient should be unconscious; but this unfortunately involves first a definition of consciousness, and this definition has so far eluded psychologists and neurophysiologists alike; it is not therefore surprising that the word itself has acquired a multiplicity of meanings. Hughlings Jackson (1931) stated that "there is no such entity as consciousness: we are from moment to moment differently conscious". However, it seems that consciousness is related to integration of the central nervous system as a whole, and that this integration may involve the reception, storage, and consideration of the significance of sensory stimuli. Magoun (1961) in his article in this issue recalls the work of Bremer (1937) who showed that bulbo-spinal section, giving the so-called "encéphale isolé", still allowed cortical electrical activity that displayed a waking pattern; whereas if the section was through the mid-brain, the so-called "cerveau isolé", the record was like that of sleep. Figure 1 shows the position of these sections in the cat's brain. This work suggested that certain parts of the brain stem were involved in consciousness. Moruzzi and Magoun (1949) in one of the most exciting experiments ever performed, showed that electrical stimulation of the reticular system of the brain stem in a drowsy animal would immediately change the sleepy electrical pattern of the cortex to one of alert attention; the animal's behaviour also showed the same change. Magoun said afterwards that one of the most memorable results of the experiment was the arousal produced in the experimenter! Sensory stimuli reaching the reticular system will also cause a similar arousal response. It would seem, therefore, that the unconsciousness produced by anaesthetic agents is related to the blocking of this arousal response, and it may be that consciousness is dependent on the reception of sensory stimuli by the reticular system. When the reticular system fails to transmit these sensory stimuli the patient becomes unconscious. Magoun (1961) describes some recent work by Batzel (1960) who kept dogs alive with isolated cerebral hemispheres for periods of some months. After the first month the e.e.g. ceased to reveal the pattern associated with an unconscious animal and showed the pattern associated with an animal that was awake. It would be very interesting to know if an animal kept alive under nitrous oxide and oxygen would also show signs of returning consciousness after a similar period.

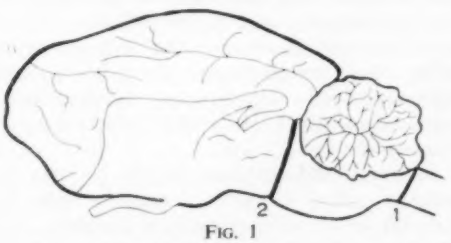


FIG. 1

Cat's brain. Section 1 produces "encéphale isolé". Section at 2 produces "cerveau isolé".

Sensory stimuli have two pathways by which they may reach the cortex. There is the classical lemniscal pathway which is specific both to modality of the stimulus applied and also to its exact location, i.e. in the lemniscal pathway the particular neurone involved in the transmission of touch from one finger will only be stimulated by touch and only from that one spot. These stimuli reach the primary reception areas of the cortex. As well as this primary and specific pathway there are secondary extra lemniscal pathways for sensory stimuli. These pathways are nonspecific both to the modality and location of stimuli. They travel up the spino-reticular, spino-tectal and spino-thalamic tracts, and a neurone involved in the stimulation of touch by one finger may be equally involved by stimulation of a joint sense in an entirely different limb (Poggio and Mountcastle, 1960). These sensory pathways are projected in a nonspecific or diffuse manner on to the cortex. The primary reception pathways, i.e. the lemniscal pathways, are only depressed by comparatively deep anaesthesia, whereas the secondary pathways are very sensitive to the effects of anaesthetic agents. It is often suggested that sensory stimuli, particularly painful stimuli, reaching the cortex during light anaesthesia—

because the primary pathways are unaffected—may cause harm by continuous bombardment. Consideration of the pathways for the transmission of pain is therefore of particular importance to the anaesthetist. Aristotle, when he propounded his doctrine of the five senses, did not include pain. He said that pain was an agony of the soul. If we put this into semi-scientific terms we might say that this means that Aristotle (Hammond, 1902) thought that pain was a generalized non-specific disturbance. Recent investigations into the pathways subserving painful stimuli have shown that there is almost certainly only a secondary nonspecific reticular pathway for pain, and more recently Poggio and Mountcastle (1960) have failed to find any neurons transmitting painful stimuli in that part of the thalamus involved in the primary lemniscal pathway for sensation. If this is so, then it would seem very unlikely, to say the least, that painful stimuli would reach the cortex during light anaesthesia, since most of the commonly used inhalational anaesthetics are also profoundly analgesic. It would appear also that unless there were some other sensation at the same time as a painful stimulus the subject would not know where it was coming from. Under normal conditions there is always some concomitant sensory or thermal stimulus with pain: for example, the cornea has been shown to be sensitive to touch and to warmth and cold (Lele and Weddell, 1956), so a patient can always tell from which part of the body his pain is coming. Aristotle, then, was perhaps perfectly correct when he differentiated pain from other sensations.

Brazier (1961) (page 194) points out that there is probably an inhibitory ascending system from the reticular system to the cortex, as well as an activating system, and that this inhibitory system appears itself to be inhibited by certain agents, particularly the barbiturates. Clutton-Brock (1960, 1961a) and Dundee (1960) have shown that the barbiturates have a facilitatory effect on the transmission of pain when this has been depressed by certain analgesic agents, and it is probable that this antanalgesic effect of the barbiturates is due to inhibition of the ascending inhibitory system. This ascending inhibitory system is affected in a U-shaped manner by the barbiturates (Brazier, 1961). The U-shaped effect is also shown by the effect of thiopentone on the response to pain (fig. 2). The facilitation of painful stimuli by the barbiturates and other substances may be important practically to the anaesthetist who is depending on this analgesic effect with certain anaesthetic agents; and it is possible that some of the ill effects ascribed to light anaesthesia may be related to the use of antanalgesic drugs. However, if painful stimuli do not cause harm during light anaesthesia, there still remains a possibility that autonomic responses, e.g. sweating, may be harmful, but there is at the moment no evidence that they are necessarily related to anaesthesia which is too light. These autonomic responses may, however, cause hypotension, which in certain patients may be dangerous.

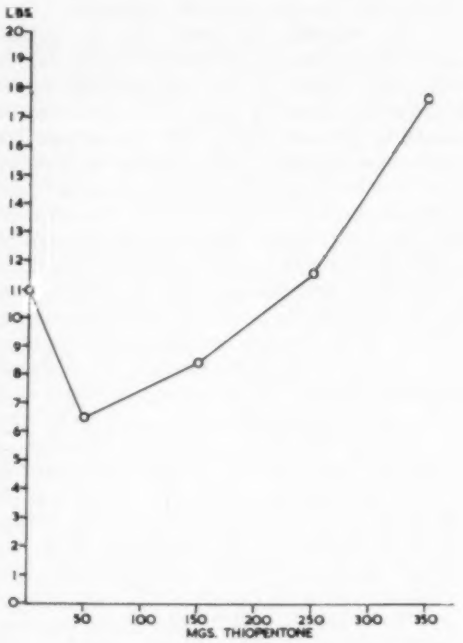


FIG. 2

U-shaped effect of thiopentone on response to pain. (Reproduced by kind permission from *Anaesthesia*.)

Magoun (1961) has also pointed out that the reticular control of afferent stimuli is under the influence of stimuli coming from the cortex, and that these stimuli form part of the mechanism whereby the subject will turn towards any stimu-

lus: the so-called "orienting" reflex. If this orienting reflex is upset, a cat can be made to fight a dog, turning his back towards his enemy (Gastaut, 1954). It has often been noticed by anaesthetists that a patient under very light anaesthesia—where the paralysis is not absolute—appears to be taking no notice of the operation but will respond to some novel but quite unimportant stimulus. The author has seen a patient, quite unresponsive to the operation, look up when he has pressed the patient's forehead to test the capillary return. It would seem, therefore, that this orienting response is not depressed very early in anaesthesia, and that where there is no pain, habituation to the operation may take place.

Practical assessment of optimum depth of anaesthesia.

The second of the problems facing the anaesthetist using very light anaesthesia is to determine whether the patient is in the optimum plane of anaesthesia. This seems to be, if anything, more difficult of solution than deciding what the optimum plane should be. There seem to be three ways of investigating this. Firstly, by looking for the responses of the patient to the stimuli arising during operation. These responses may be movement of voluntary muscles or of autonomic responses; but since there is an inverse relationship between the dose of relaxant drugs and the depth of anaesthesia for any given amount of movement by the patient, this movement is of very little help, i.e. a lightly anaesthetized patient will require a large dose of relaxant drug to prevent other than slight movements. These movements may occur under rather deeper anaesthesia with less relaxant drug. Autonomic responses seem to be of even less help though there is scope for research into the effects of stimuli on such matters as sweating, blood pressure and other changes in relation to the type and depth of anaesthesia used. Furthermore, there is enormous variation from patient to patient in their responses to stimuli at what appears to be the same level of anaesthesia. For example, the author has seen a patient being operated on for the removal of an aortic aneurysm who, when the effects of the relaxant drug were wearing off somewhat, was able to reply by nodding his head to the question, "Are you comfortable?" The surgical team was somewhat surprised at the question and even more surprised at the answer. This patient continued under these conditions for 6 hours and it was remarked after the operation that he was particularly fit and well. He did not move, nor were there any obvious autonomic responses to what was certainly very considerable operative manipulation in his abdomen. This patient remembered nothing whatever of his experience. The author has also seen profound sweating in a patient for no particular reason during a trivial operation, and the same can be said of muscular movement. It may well be that with certain anaesthetic agents there is a level where responses are augmented, and that one can be on the light—and perhaps the right—side of trouble.

The second investigation anaesthetists may make is by questioning the patient afterwards about his experience. A patient may have amnesia but this does not mean that he did not suffer. Amnesia surely is not an adequate substitute for anaesthesia! The patient's memory afterwards of the event does not seem to be particularly related to the amount of response at the time of operation; at least, in the author's experience.

Lastly, he may use electroencephalography and the various extensions of this technique which have been recently developed (Clutton-Brock, 1961b). The various planes of anaesthesia with various anaesthetic agents have been related to various e.e.g. changes. With cyclopropane, for example, these changes seem to bear a satisfactory relationship to changes in blood concentrations (Possati et al., 1953). With thiopentone, however, it has recently been shown that this relationship often does not hold in man. In many patients, blood concentrations rose while the e.e.g. level of anaesthesia remained the same (Brand, 1960). Whether the actual depth of anaesthesia remained the same despite the rise in the blood concentration of the drug is a matter for further investigation and also probably involves further definition of the depth of anaesthesia. With nitrous oxide the author has failed to find any constant relationship between the depth of anaesthesia and the e.e.g. pattern. During anaesthesia in man there is often a persistent alpha rhythm throughout the whole operation; but this alpha rhythm has not, so far, been found in volunteers anaesthetized with

nitrous oxide and adequate oxygen (without premedication), though the numbers of volunteers so far anaesthetized in this manner is not yet large enough for any firm conclusion.

A vast amount of research is needed to study the effects of very light planes of anaesthesia on the central nervous system.

REFERENCES

Artusio, J. F. jnr. (1955). Ether analgesia during major surgery. *J. Amer. med. Ass.*, **157**, 33.

Batzel, H. L. (1960). Electroencephalographic synchronization and desynchronization in the chronic "cerveau isolé" in the dog. *E.E.G. clin. Neurophysiol.*, **12**, 421.

Brazier, M. A. B. (1961). Some effects of anaesthesia on the brain. *Brit. J. Anaesth.*, **33**, 194.

Bremer, F. (1937). L'activité cérébral au cours du sommeil et de la narcose. Contributiòn à l'étude du mechanisme du sommeil. *Bull. Acad. roy. Méd. Belge.*, **2**, 68.

Brand, B., Marke, L. C., Mazzia, V. D. B., Van Posnak, A., Artusio, J. F. jnr., Burns, J. J., and Papper, E. M. (1960). Lack of correlation between electroencephalographic effects and plasma concentrations of thiopentone. 2nd World Congress of Anesthesiologists, Toronto, and *Brit. J. Anaesth.* (1961), **33**, 92.

Clutton-Brock, J. (1957). The cerebral effects of overventilation. *Brit. J. Anaesth.*, **29**, 111.

—— (1960). Some pain threshold studies with particular reference to thiopentone. *Anaesthesia*, **15**, 71.

—— (1961a). Pain and the barbiturates. *Anaesthesia*, **16**, 80.

—— (1961b). Electroencephalography. *Brit. J. Anaesth.*, **33**, 205.

Dell, P., and Bonvallet, M. (1954). Controle direct et réflexe de l'activité du système reticulé activateur ascendent du tronc cérébral par l'oxygène et le gaz carbonique de sang. *C.R. Soc. Biol. (Paris)*, **148**, 855.

Dundee, J. W. (1960). Alterations in response to somatic pain associated with anaesthesia. II: The effect of thiopentone and pentobarbitone. *Brit. J. Anaesth.*, **32**, 407.

Editorial, *Brit. med. J.* (1880), **2**, 628.

Gastaut, H. (1954). *Brain Mechanisms and Consciousness*, p. 419. Oxford: Blackwell.

Geddes, I. C., and Gray, T. S. (1959). Hyperventilation for the maintenance of anaesthesia. *Lancet*, **2**, 4.

Hammond, W. A. (1902). *Aristotle's Psychology: Treatise on the Principle of Life*. London: Sonneuschein.

Jackson, J. H. (1931). *Selected Writings of John Hughlings Jackson*, Ed. James Taylor. London: Hodder and Stoughton.

Lele, P. P., and Weddell, G. (1956). The relationship between neurohistology and corneal sensibility. *Brain*, **79**, 119.

Loder, R. E. (1957). Inadequacy of general anaesthesia for abdominal operations. *Lancet*, **2**, 468.

Magoun, H. W. (1961). Brain mechanisms for wakefulness. *Brit. J. Anaesth.*, **33**, 183.

Moruzzi, G., and Magoun, H. W. (1949). Brain stem reticular formation and activation of the E.E.G. *Electroenceph. clin. Neurophysiol.*, **1**, 455.

Poggio, G. F., and Mountcastle, V. B. (1960). A study of the functional contributions of the lemniscal and spinothalamic systems to somatic sensibility. *Bull. Johns Hopk. Hosp.*, **106**, 266.

Possati, S., Faulconer, A. jnr., Bickford, R. G., and Hunter, R. C. (1953). Electroencephalographic patterns during anaesthesia with cyclopropane. *Anesth. and Analg.*, **32**, 130.

Brit. J. Anaesth. (1961), **33**, 219

THE EVOLUTION OF PREMEDICATION

BY

WILLIAM M. SHEARER
The Royal Infirmary, Dundee, Scotland

(Continued from Vol. 32, No. 11)

PREMEDICATION in 1920 was not regarded as an indispensable preliminary to anaesthesia; although it was practically a routine to give atropine before ether, surgical opinion was not wholly in favour of pre-anaesthetic sedation. The respiratory depression caused by morphine sometimes made it difficult to attain any depth of anaesthesia. Barton (1919) wrote: "Alkaloids have now been used as a preliminary to the administration of anaesthetics for some years. There is a general opinion amongst anaesthetists as to their value. Amongst surgeons, however, there is still some divergence of view. A few unfortunate experiences early in their use raised the cry 'scopolamine belly', 'morphine rigidity', and so forth; the method is decried and abandoned." The drugs available for pre-anaesthetic use were almost limited to atropine, hyoscine, morphine and Omnopon (papaveretum); children were usually given only atropine.

During the 1920s there were three developments, the course of which will first be described. (1) The word "premedication" came into use. (2) Heavy sedation before anaesthesia (called "basal narcosis") was suggested and drugs were introduced for its practice. (3) The pre-operative sedation of children was initiated.

The word "premedication".

This was used verbally for many years before it was accepted by the editors of journals, the terms pre-anaesthetic or preliminary medication being thought more correct; naturally it was found in American articles earlier than in those by British authors. Boyle (1917) writing in the *Lancet*, described his use of a "preliminary injection" of morphine, atropine and hyoscine. When the article was reprinted in the *American Year Book of Anaesthesia and Analgesia*, the editor McMechan (1920a) inserted "Pre-medication" in a paragraph heading. In the same year McMechan (1920b), as editor of the anaesthetic supplement of the *American Journal of Surgery*, described the results of a questionnaire which included, "Do you use Premedication? If so, what?" These are the earliest records of the word I have as yet found. Gradually it appeared more frequently, but neither Gwathmey (1925) nor Flagg (1928) used it in their textbooks. During 1926 a number of American anaesthetists visited Britain and the first record of its use which I have found in this country was in an address by McKesson (1926) at a meeting of the Section of Anaesthetics of the British Medical Association in Nottingham. The word made slow progress. The *Lancet* (1928a) in an annotation on "Drugs before Anaesthesia" contained the statement: "The advantages of using hypodermic injections of various drugs before the administration of anaesthetics are not admitted by everyone. There are anaesthetists who never employ this 'premedication' and there are surgeons who strongly object to it." The same year, however, the *Lancet* (1928b) headed an annotation "Premedication with Anaesthesia".

"Premedication" was used in the title of a paper by McKesson and Clement (1925). The first article I have found by a British author which included the word as a heading was by Sington (1929) writing on "Pre-medication with Paraldehyde in Children". Hewer (1932), in the first edition of *Recent Advances in Anaesthesia* used "pre-medication". In later editions the hyphen was dropped and "premedication" had entered the language.

The rise and fall of basal narcosis.

At first no distinction was made between premedication and basal narcosis, although the practice of rendering patients unconscious in bed did not arise from the use of the usual premedicant drugs. Gwathmey (1914), advocating rectal

oil-ether and paraldehyde anaesthesia, described the enema given in bed to produce unconsciousness as "the preliminary medication", and the enema given in the theatre as "the induction of anaesthesia". Anaesthetists, however, did not readily accept the idea of unconsciousness before the administration of the anaesthetic proper, and the use of basal narcosis in Great Britain awaited the stimulus of Rowbotham (1928). He used rectal paraldehyde and, acknowledging the inspiration of Gwathmey's work described his object to the Section of Anaesthetics of the Royal Society of Medicine thus: "The customary $\frac{1}{6}$ gr or $\frac{1}{4}$ gr of morphine is an uncertain and usually insufficient dose. My chief object was to find a way of protecting the nervous system by producing in the patient such a profound sleep before administration of the anaesthetic and whilst he was still in bed that it would be impossible to arouse him . . . the patient would have no knowledge of the induction . . . and waken some hours after the operation." In the discussion Mennell (1928) was critical and an annotation in the *Lancet* (1928b) ran as follows: "The discussion makes it plain that there is still a good deal of difference of opinion with regard to the advantages of using sedative drugs before the administration of anaesthetics proper . . . all were agreed on the amount of extra care and trouble that devolves on the nursing staff in institutions where effective premedication is widely employed."

However, basal narcosis caught the popular imagination and several drugs were soon in use for its accomplishment. Avertin (bromethol), referred to in the *Lancet* (1927) as E.107 which was at that time being tried out in Germany, became available here in 1929. Initially regarded as an anaesthetic, it was soon described as a basal narcotic. Sodium Amytal (amylobarbitone) and Nembutal (pentobarbitone) came from America and were the first barbiturates to come into established use in anaesthesia and the first drugs to be popularly and safely used for the intravenous and oral induction of basal narcosis. In the English literature the use of Amytal and of Nembutal was described by Zerfas (1930) and Magill (1931) respectively. They rapidly became popular and Boyd (1932) reported the use of Nembutal in over one thousand patients in St. Bartholomew's Hospital, stating: "Both oral and intravenous routes were used, the large majority received it orally."

The practice considered ideal during the 1930s was to render the patient unconscious with a rectal or intravenous drug before transfer to the theatre and to complete anaesthesia with a small amount of inhalation anaesthetic, recovery of consciousness being delayed until some time after return to bed. Ashworth (1936a) described it as "undoubtedly the most important development of anaesthesia during the present century". This view has to be judged against the unpleasantness of a nitrous oxide-oxygen-ether induction and the postoperative sickness which followed prolonged deep ether anaesthesia. Despite the enthusiasm, however, basal narcosis never became a common hospital practice, and foundered on the responsibility placed on the nursing staff. Macintosh and Pratt (1940a), when the practice was losing favour and being criticized in many ways, stated: "The one tenable argument against most basal anaesthetics is that the prolonged period of unconsciousness which they produce increases the period, pre- and post-operative, during which the patient must not be left without skilled supervision."

The anaesthetist became less willing to depend on others for the maintenance of a clear airway and when the use of muscle relaxant drugs with light anaesthesia became routine, the advantages of early recovery of consciousness was at once apparent, and basal narcosis, as it was understood in the thirties, fell out of use except for special occasions.

The development of paediatric premedication.

Hewer (1923) recommended that children should be given atropine alone, by hypodermic injection half an hour before operation, stating, "1/150 grain is a good average dose". Sington (1926) described the custom in the Hospital for Sick Children, Great Ormond Street, of giving only atropine, by mouth. He was against hypodermic injections in children, did not refer to sedation and stated that much trouble was taken to make the induction pleasant. Sington (1929) followed the fashion of the times and recommended basal narcosis with rectal paraldehyde, stating: " . . . though at first it was only given to nervous children, it is now in the majority of cases given as an act of kindness to the children.

They went to sleep in bed and awoke many hours later in bed with no knowledge of anything unpleasant having occurred." Thus the induction was no longer disturbed by emotional scenes. During the 1930s many thought that there could be no argument about the necessity for basal narcosis in children. Ashworth (1936b) wrote: "An anaesthetist witnesses few scenes more disturbing than the abject terror so often displayed by the unfortunate child. It is hardly an overstatement to say that excepting in case of urgency no conscious child should ever see the theatre or be submitted to the terrors associated with the induction of anaesthesia."

Mallinson's (1942) statement was: "The ideal to be aimed at is that the child should fall asleep . . . and awaken again afterwards in its own bed." This ideal, expressed against the background of induction methods in the thirties, persisted longer in the management of children than it did in anaesthesia for adults. Rectal thiopentone, introduced by Weinstein (1939), arrived too late to achieve popularity for basal narcosis in adults. Its special value in children was described by Burnap, Gain and Watts (1948) and by Mark, Fox and Burstein (1949), and it displaced paraldehyde and bromethol.

With the waning of enthusiasm for basal narcosis, however, the view that the pre-anaesthetic sedation of children should be light was re-asserted. Respiratory depression and postoperative unconsciousness were too big a price to pay for heavy sedation and developments in anaesthesia such as the disappearance of the nightmare induction limited the problem to the 2–4 age group. Belton and Leigh (1950) wrote: "We are *not* happy when we see our patients sleep soundly for several hours post-operatively; we find their respiratory and circulatory systems much better if they rouse, cough or cry a little on the operating table before returning to the ward." Whereas Mallinson (1942) could state, "the sinister significance of psychological damage has received wide recognition", the existence of mental trauma was now doubted, or at least that it resulted from the anaesthetic. Junkin (1956), writing on night fears and other psychological disturbances attributed to anaesthesia, stated: "I believe they might as properly be blamed on the separation from a fond and indulgent parent. . . . In my thirty years of experience in pediatric anesthesia 'trauma' has not been of sufficient moment for our child psychologists to do more than talk vaguely about it." Furthermore, arguments were put forward that mentally as well as physically it was not wholly an advantage for the child to be asleep before induction of anaesthesia (Rees, 1958).

From no sedation in 1920 the pendulum swung to basal narcosis as the ideal in 1930. Now it was back again and as much stress was being laid on the psychological approach to the child as on his sedation. Premedication now had to suit the anaesthetist and, if he had the time and ability to talk a child into an anaesthetic, little else was necessary in the way of sedation. Sometimes it even seemed that an excuse had to be offered for sedation. Beard (1959) stated that " . . . pressure of work may make the establishment of any sort of rapport almost impossible and if sedation is needed recourse must be had to drugs". Smith (1959), after mentioning the time required to induce unsedated children, wrote: "This time would be invested gladly were it not possible to do the job more effectively by medication. For safety and simplicity the use of sedation seems definitely indicated, provided care is taken to avoid overdosage and depression."

Most anaesthetists, although preferring the 2–4 age group to be asleep before reaching the theatre, desire older children to be rousable and rational but sleepy and quiet. There is little agreement about how to attain this state. Waters (1938) had recommended morphine and scopolamine. He gave no dosage, stating: "Careful individualization of choice of drugs as well as doses will develop in the physician a skill far more satisfactory than any attempt at routinization." Leech (1935) had provided a dose by age table for morphine and scopolamine and Baker and Chivers (1941) used this to calculate a dose by age table for papaveretum and scopolamine. Anderson (1951) suggested a dose by weight table for use in general surgery. Recommending larger amounts than those previously employed, she described the pre-operative condition of children thus: "Never has there been any cause for anxiety. The children have been drowsy but co-operative and with a dry respiratory tract." Anderson's dose by weight table has been widely used and a comparison with doses of papaveretum and scopola-

TABLE I

Age	Baker and Chivers (1941) Average weight (lb.)	Papaveretum grain	Hyoscine grain	Anderson (1951) Weight lb.	Papaveretum grain	Hyoscine grain
2–4	31	1/18–1/15	1/600	28	1/9	1/450
4–8	42	1/12–1/9	1/450	42	1/6	1/300
8–12	61	1/9	1/450	56	1/4	1/200
12–16	90	1/6	1/300	70	1/3	1/150

mine previously prescribed illustrates the decline in the prejudice against giving of opiates to children (table I).

Pentobarbitone (Nembutal) and quinalbarbitone (Seconal, introduced in 1935), usually given orally, have continued in popularity. Postoperative restlessness is invariably cited as a disadvantage and morphine is suggested for its control. Anderson (1959) stated that "promethazine, combined with other drugs, is proving as useful in the premedication of children as in adults". Recently there has been a vogue for thiopentone suppositories, but many are against the giving of drugs rectally to children.

The present position of premedication in children has been described by Smith and Jeffries (1959): "One of the most confusing and unsatisfactory aspects of pediatric anaesthesia is that of pre-operative sedation. Although most anaesthetists agree that sedation is indicated, no two agree on what or how much should be given or when or by what route it should be administered."

The changing aims of premedication.

As methods of anaesthesia altered, ideas about what might be achieved by premedication changed. While chloroform was popular, preoperative atropine was given to prevent reflex cardiac arrest. When ether replaced chloroform the anaesthetist was enabled to give a smooth ether anaesthetic by the use of morphine, hyoscine and atropine pre-operatively. In non-abdominal work the respiratory depression caused by morphine was no handicap and the patient was spared pre-operative worry and an unpleasant induction. Soon a virtue was made of what had been regarded as a necessity and Barton (1919) stated: "The main object of preliminary narcotics is, in my view, the patient's comfort and safety." For many years, however, the patient's comfort was regarded only as a subsidiary object and sedative premedication was given to reduce metabolism. In America, nitrous oxide and oxygen had become a usual anaesthetic for major surgery and in its practice premedication was essential. Clement (1939), in his book on nitrous oxide-oxygen anaesthesia which described the McKesson-Clement methods, emphasized in italics the sentence, *"It is futile to attempt the use of nitrous oxide-oxygen routinely for major surgery without particular care being given to the premedication."* Guedel (1922) explained the action of morphine in premedication thus: "We give morphine alone or in combination as the preanaesthetic drug of choice for nitrous oxide-oxygen anaesthesia. Why? As a metabolic inhibitor morphine occupies first place in our medical armamentarium. By inhibiting metabolism it decreases tissue oxygen demand and thereby increases available nitrous oxide space within the cell." Reduction of metabolism soon became the justification for sedation before *any* anaesthetic. Reflex irritability varied with metabolic rate and depth of anaesthesia was proportional to reduction of metabolism; if metabolism were reduced beforehand, less anaesthetic was required to reach a given depth and the safety of the anaesthetic increased. Premedication and anaesthesia were parts of a continuous process. Alexander and Cullen (1936) wrote: "The classical discussion of Guedel on the role of pre-operative medication in its effect on reflex irritability and metabolism is the basis of the modern conception of the subject . . . a consideration of the factors influencing the metabolism of the patient appears the only basis for the intelligent administration of morphine." Minnitt and Gillies (1945), while describing also the subsidiary benefits of premedication, stated: "The primary role, therefore, of premedication by depressant drugs—morphine, bromethol, etc., is to lower the patients metabolic rate, and so render him more susceptible to

the further depressant influence of whatever anaesthetic agent may follow." Although in later years doubt was cast on the ability of normal premedication to lower the metabolic rate it was again a change in the methods of anaesthesia, occurring between 1940 and 1950, which had the greater influence on the aims of premedication.

The position in 1940.

Macintosh and Pratt (1940b) writing on premedication stated: " . . . it must not be forgotten that even under the best conditions an inhalation anaesthetic can rarely be described as pleasant". Nitrous oxide oxygen-ether had become the routine anaesthetic throughout the country. Preanaesthetic atropine was essential and preliminary sedation was generally desired. This was the heyday of routine premedication and its omission would delay the patient's transfer to the theatre and cause recrimination in the ward. Although lip service was paid to individual treatment it was not uncommon for all adult patients prepared for major surgery to receive morphine 10 mg (1/6 grain) and atropine 0.6 mg (1/100 grain), or papaveretum 20 mg (1/3 grain) and hyoscine 0.4 mg (1/150 grain). The patient did not regain full consciousness for an hour or two after a major operation. The ether caused some sickness; that caused by morphine was not appreciated so readily.

The main object of routine premedication was to enable the anaesthetist to give a smooth anaesthetic and there were those who did not admit that it was for the patient's benefit. Minnitt (1939), for example, was reported as saying that in a series of major operations in which no premedication was given, he came to the conclusion that the after condition of the patients was better than in those who had been premedicated!

The position in 1950.

The preliminary injection of intravenous thiopentone was now routine; the need for sedation to smooth the unpleasantness of induction had gone. The use of curare had banished ether from routine maintenance in abdominal surgery; the need for pre-operative atropine was not so urgent. The changed methods had affected premedication in other ways. Second plane anaesthesia was now exceptional. When a patient was immobilized with relaxant and anaesthesia maintained with nitrous oxide and oxygen, depth of anaesthesia and reduction of metabolism had lost their importance. The patient could now regain consciousness at the end of the operation. If he awoke before leaving the theatre precincts, the anaesthetist was no longer dependent on the nursing staff to maintain a clear airway. d'Abreu (1959) stated: "On one point I am adamant. The patient must speak to me before he leaves the theatre." In some regions, too the necessity for reporting a postoperative death as a death under anaesthesia depended on whether or not consciousness had been regained before death (Lawrie, 1958). This led anaesthetists to desire very strongly that a patient should awaken soon after a major operation. Postoperative vomiting, now less common, was more noticed and the part played by preoperative morphine was beginning to be recognized.

Such factors weighed against pre-operative sedation, but if the original objects of premedication had gone and interest in the reduction of metabolism had declined, other aims had taken their place. Beecher (1955) wrote: "It is fair to say that premedication has two general purposes (1) to present an acquiescent, well rested, serene patient to the surgeon, and (2) to minimize in so far as possible the hazards of anaesthesia and surgery." He suggested that 1½ grains of pentobarbitone should replace the traditional injection of morphine, but many anaesthetists consider that Beecher's aims are more readily attained by recently introduced drugs.

The use of pethidine as a substitute for morphine in premedication was described by Rovenstine and Batterman (1943) who claimed that it had all the virtues of morphine but caused less respiratory depression, less postoperative nausea and dried secretions more effectively. During the early 1950s techniques of anaesthesia were described using phenothiazine derivatives and pethidine as the principal or frequently the only agents. This practice had a short vogue but led to an increased use of these drugs pre-operatively. Beecher's first aim in premedication was to have the patient awake but unworried. Hopkin (1957) and his colleagues explained that this was possible with the new drugs by "the shift of the emphasis from the cortex to the subcortex as the primary target for the suppression of conscious aware-

ness". They stated: "Promethazine (and chlorpromazine) has the unique property of depressing the arousal mechanism of the reticular activating system without affecting the activity of the cortical system." Foster (1960), alluding to the many reports on the use of promethazine in premedication, said "all agree that a dose of 50 mg given with pethidine 50 or 100 mg and atropine 0.4 mg before operation produce a calm patient, sleepy but rousable."

It was also claimed that by the use of these drugs Beecher's second aim in premedication could be realized and that the hazards of anaesthesia were reduced. A subduing effect on the bronchial and laryngeal reflexes was invariably reported. Hopkin et al. (1957) wrote: "The unpredictable attacks of coughing and laryngospasm which may mar an otherwise normal thiopentone induction are seldom encountered." Dinnick (1954), speaking of the anaesthetic management of asthmatic and bronchitic patients, said: "Premedication with promethazine makes them much more controllable under anaesthesia. Not only are the laryngeal reflexes less active, but, even more noticeable, there is less tendency for bronchospasm to occur in response to anaesthetic stimuli." Foster (1960) wrote that, compared with papaveretum and hyoscine, "there is a rapid return of reflexes postoperatively and a decreased need for postoperative analgesics for the first twelve hours, with less postoperative nausea and vomiting". Gray and Riding (1957), writing on anaesthesia for mitral valvotomy, illustrated the trend in premedication; for example, in 1950 they gave morphine and atropine; in 1955, papaveretum and hyoscine. In 1957 they wrote: "This premedication has become less popular because there is a tendency towards delay in full recovery of consciousness. For this reason promethazine in combination with atropine is now more generally preferred."

The position in 1960.

In a criticism of established methods of premedication with morphine and atropine, Beecher (1955) wrote: "Empirical procedures firmly established in the habits of good doctors have a life, not to say immortality of their own." Current literature suggests that the majority of patients having major surgical operations receive morphine and atropine, or papaveretum and hyoscine. The use of promethazine and pethidine is increasing and it has been found economic to provide various combinations of promethazine, pethidine, atropine and hyoscine in single ampoules for premedication. The popularity of halothane has stimulated the use of atropine because the early literature on halothane stressed the necessity of including atropine in the premedication.

The present popular method of anaesthesia, with immobility depending on the use of relaxant drugs, and nitrous oxide (and oxygen) the only inhalation anaesthetic, has renewed interest in premedication. A new generation of anaesthetists, intent upon the pre-operative examination and the immediate postoperative welfare of the patients, has become responsible for pre- and postoperative sedation. They prescribe individual premedication rather than leave it to be given routinely, as had been the practice for almost fifty years.

ACKNOWLEDGMENTS

I am indebted to my colleague Dr. I. Murray Lawson for his constant helpful criticism and to the Medical Information Division of Messrs. May & Baker for information about the early use of the barbiturates in anaesthesia.

REFERENCES

d'Abreu, A. L. (1959). Post-war development of anaesthetic and surgical techniques in cardiac surgery. Lecture to Scottish Society of Anaesthetists, Edinburgh, February 20, 1960 (not published).

Alexander, F. A. D., and Cullen, S. C. (1936). Preanaesthetic medication. *Amer. J. Surg.*, **34**, 428.

Anderson, S. M. (1951). Use of depressant and relaxant drugs in infants and children. *Lancet*, **2**, 965.

—— (1959). Principles and practice of paediatric anaesthesia. *General Anaesthesia*, Vol. 2, p. 160, London: Butterworth.

Ashworth, H. K. (1936a). *Practical points in Anaesthesia*, p. 120. London: Churchill.

—— (1936b). The use of Avertin for the production of basal narcosis in children. *Arch. Dis. Childh.*, **11**, 157.

Baker, A. H. L., and Chivers, E. M. (1941). Opium as a pre-anaesthetic sedative in children. *Lancet*, **1**, 171.

Barton, G. A. H. (1919). Alkaloids in anaesthesia; their use and abuse. *Practitioner*, **103**, 253.

Beard, A. J. W. (1959). The principles of premedication. *General Anaesthesia*, Vol. 1, p. 263. London: Butterworth.

Beecher, H. K. (1955). Preanesthetic medication. *J. Amer. med. Ass.*, **157**, 242.

Belton, M. K., and Leigh, D. (1950). Premedication in pediatric anesthesia. *Curr. Res. Anesth.*, **29**, 74.

Boyd, A. M. (1932). The use of Nembutal as a basal hypnotic before general anaesthesia based upon over 1,000 cases. *St. Bart's Hosp. Rep.*, **65**, 283.
Boyle, H. E. G. (1917). The use of nitrous oxide and oxygen with rebreathing in military surgery. *Lancet*, **2**, 667.
Burnap, R. W., Gain, E. A. and Watts, E. H. (1948). Basal anaesthesia in children using sodium pentothal by rectum. *Anesthesiology*, **9**, 524.
Clement, F. W. (1939). *Nitrous Oxide-oxygen Anaesthesia*, p. 47. London: Kimpton.
Dinnick, O. P. (1954). In discussion on antihistamines and anaesthesia. *Proc. roy. Soc. Med.*, **47**, 415.
Flagg, P. J. (1928). *The Art of Anaesthesia*, 4th ed. Philadelphia: Lippincott.
Foster, V. A. (1960). The antihistamine and tranquilliser or ataractic drugs. *A Practice of Anaesthesia*, p. 701. London: Lloyd-Luke.
Gray, T. C., and Riding, J. E. (1957). Anaesthesia for mitral valvotomy. *Anaesthesia*, **12**, 129.
Guedel, A. E. (1922). The faultiness of rapid induction of anesthesia with nitrous oxide. *Curr. Res. Anesth.*, **1**, 59.
Gwathmey, J. T. (1914). *Anesthesia*, 1st ed., p. 458. New York: Appleton.
—— (1925). *Anesthesia*, 2nd ed. New York: Macmillan.
Hewer, C. L. (1923). *Anaesthesia in Children*, p. 3. London: H. K. Lewis.
—— (1932). *Recent Advances in Anaesthesia and Analgesia*, 1st ed., p. 29. London: Churchill.
Hopkin, D. A. B., Hurter, D., and Jones, C. M. (1957). Promethazine and pethidine in anaesthesia. *Anaesthesia*, **12**, 276.
Junkin, C. I. (1956). Preoperative medication for Children. *Canad. Anaesth. Soc. J.*, **3**, 209.
Lancet (1927). Annotation: E.107. *Lancet*, **1**, 718.
—— (1928a). Annotation: Drugs before anaesthesia. *Lancet*, **1**, 352.
—— (1928b). Annotation: Premedication with anaesthesia. *Lancet*, **2**, 1252.
Lawrie, R. (1958). Deaths under anaesthesia. *Brit. J. Anaesth.*, **30**, 85.
Leech, B. C. (1935). Preanesthetic medication in children. *Curr. Res. Anesth.*, **14**, 283.
Macintosh, R. R., and Pratt, F. B. (1940a). *Essentials of General Anaesthesia*, p. 100. Oxford: Blackwell.
—— —— (1940b). *Essentials of General Anaesthesia*, p. 91. Oxford: Blackwell.
McKesson, E. I. (1926). Discussion on newer gas anaesthetics. *Brit. med. J.*, **2**, 1113.
—— Clement, F. W. (1925). Some relations of metabolism to premedication and anaesthesia. *Brit. J. Anaesth.*, **3**, 32.
McMechan, F. H. (1920a). *American Year Book of Anesthesia and Analgesia*, 1917–18, **2**, 245.
—— (1920b). Results of a survey by the National Anesthesia Research Society of a selected group of hospitals to determine the status of anaesthetic service. *Amer. J. Surg.*, Q. Suppl., **34**, 123.
Magill, I. W. (1931). Nembutal as a basal hypnotic in general anaesthesia. *Lancet*, **1**, 74.
Mallinson, B. (1942). Anaesthetic problems in children. *Med. Press.*, **208**, 416.
Mark, C. L., Fox, J. L., and Burstein, C. L. (1949). Preanaesthetic hypnosis with rectal pentothal in children. *Anesthesiology*, **10**, 401.
Mennell, Z. (1928). In discussion on preliminary medication in anaesthesia. *Proc. roy. Soc. Med.*, **22**, 658.
Minnitt, R. J. (1939). In discussion on premedication. *Proc. roy. Soc. Med.*, **33**, 294.
—— Gillies, J. (1945). *Text Book of Anaesthetics*, p. 73. Edinburgh: Livingstone.
Rees, G. J. (1958). The anaesthetist in the paediatric unit. *Modern Trends in Anaesthesia*, p. 210. London: Butterworth.
Rovenstine, E. A., and Batterman, R. C. (1943). The utility of Demerol as a substitute for the opiates in preanaesthetic medication. *Anesthesiology*, **4**, 126.
Rowbotham, E. S. (1928). Preliminary medication in anaesthesia. *Proc. roy. Soc. Med.*, **22**, 653.
Sington, H. (1926). Discussion on anaesthetics in children. *Proc. roy. Soc. Med.*, **19**, 1.
—— (1929). Pre-medication by paraldehyde in children. *Proc. roy. Soc. Med.*, **22**, 1197.
Smith, R. M. (1959). *Anesthesia for Infants and Children*. St. Louis: Mosby.
—— Jeffries, M. (1959). The evaluation of sedative agents for preoperative use in children. *Curr. Res. Anaesth.*, **38**, 166.
Waters, R. M. (1938). Pain relief in children. *Amer. J. Surg.*, **39**, 471.
Weinstein, M. L. (1939). Rectal pentothal sodium; a new pre- and basal anesthetic drug in the practice of surgery. *Curr. Res. Anesth.*, **18**, 221.
Zerfas, L. G. (1930). Sodium Amytal and other derivatives of barbituric acid. *Brit. med. J.*, **2**, 897.

CORRESPONDENCE

EPIDURAL BLOCK IN OLD PEOPLE

Sir,—I was interested to read Dr. Mostert's article (*Brit. J. Anaesth.*, 1960, **32**, 613), confirming the possibility of a total epidural block occurring in the elderly patient. It is rather a sweeping statement to suggest that this procedure should be replaced by subarachnoid spinal analgesia. For many years epidural analgesia has been used in the elderly, poor risk subject in place of spinal analgesia, because of the inherent dangers and disadvantages of the latter. Although headache is less common in the elderly following subarachnoid spinal block, surely this contention cannot hold good in the patient with pre-operative respiratory disease. If there is coughing, dyspnoea and the use of the accessory muscles of respiration, this must result in leakage of cerebrospinal fluid and consequent headache in the postoperative stage.

Mostert quotes two instances of untoward motor paralysis affecting the respiratory muscles in the same patient. In both instances a 2 per cent solution of lignocaine was used and this strength inevitably causes motor paralysis in the amounts used. This point is emphasized by Bromage (1954), who states that solutions of lignocaine stronger that 1.25 per cent cause increasing degrees of motor paralysis. Granted that there is a greater intensity of epidural block after all analgesic solutions with increasing age, one should on that account use lower concentrations of the drug than one employs in younger patients, to produce the benefits of a differential block. It is rather more difficult to explain the motor paralysis that occurred in Morrow's patient (*Brit. J. Anaesth.*, 1959, **31**, 359), when a 1.5 per cent solution of lignocaine was used. However, there probably was a total spinal block in this case as evidenced by the cranial nerve involvement and the loss of consciousness. If it was a total epidural block, it proves the necessity for using a lower concentration than 1.5 per cent lignocaine in the elderly.

In 1955–56 at Tel Hashomer Hospital, Israel, I used a 1.5 per cent solution of lignocaine to anaesthetized twelve patients, whose ages were from 55 to 80 years, most of whom had chest disease ranging from bronchitis to severe emphysema and in no instance was there any respiratory or motor paralysis.

I recently anaesthetized a patient, aged 42, at this hospital for fibroids extending to the epigastrium. Thirty ml of 1.5 per cent lignocaine was used with a 15 degree Trendelenburg tilt. Analgesia was complete to the level of the fourth cervical segment with absolutely unimpaired respiration. As measured with a Ruben valve and a rebreathing bag, this was 8 l./min.

The indication par excellence for an epidural block is the elderly patient with chest disease requiring an upper abdominal operation. If 1 to 1.5 per cent lignocaine solution is used and the dosage varied according to the height of the patient a satisfactory sensory block does result. Even if a total epidural block develops in the occasional patient, only sensory block usually occurs, for which no treatment is required. There are thus valid reasons for the retention of the use of epidural analgesia in the elderly. Mostert's work shows the need for precautionary measures in such patients These should include a low concentration of solution and reduced dosage. With a consideration of these factors, I am convinced that epidural analgesia remains one of the safest anaesthetic procedures in the elderly.

S. Bobrow
Johannesburg

REFERENCE

Bromage, P. R. (1954). *Spinal Epidural Analgesia*, 1st ed. Edinburgh: Livingstone.

Sir,—I would like to take issue with Dr. Mostert (*Brit. J. Anaesth.*, 1960, **32**, 613) who advises against the use of the technique of extradural analgesia in old people.

Surely this excellent technique could well be applied to old people using a continuous extradural method with a catheter, titrating the dose and volume of analgesic solution to the patient's needs.

To cite an example: A 72-year-old hypertensive male with angina having a prostatectomy was

given an initial dose of 8 ml 1.5 per cent lignocaine with adrenaline 1 : 250,000 through a Tuohy needle, after which a catheter was introduced into the extradural space. Analgesia was quite sufficient and all he needed was thiopentone 250 mg to keep him asleep, and vasopressor drugs to keep his systolic pressure above 110 mm Hg.

With a "single injection" used on this patient, he would have received a considerably larger volume which in his case would have been excessive. Using a catheter, smaller judicious doses can be given and, if these are not sufficient to produce a block commensurate with the surgeon's requirements, additional amounts can be added as necessary.

H. K. DUBE
General Hospital, Southend-on-sea

THE FIRST ENDOTRACHEAL INTUBATION

Sir,—The publication of "Evolution of Endotracheal and Endobronchial Intubation" by G. M. J. White (*Brit. J. Anaesth.*, 1960, **32**, 235) was appreciated by this reader. I was rather surprised that neither Davison (1951) nor Mushin and Rendell-Baker (1953) were listed in his references. A letter in your July issue from Dr. Armstrong Davison (1960) reviews his article and further addition is not necessary. Chapter VI of Mushin and Rendell-Baker (1953) covers a large gap in White's paper and should be mentioned. Perhaps attention should be drawn especially to the plates (figs. 14 and 13, Mushin and Rendell-Baker, 1953) from Curry (1792) illustrating an endotracheal tube in situ and showing a tracheal cannula. Figure 14 in this chapter is the earliest plate I have found of an endotracheal tube in situ —Stanley Sykes may have an earlier reference. Figure 1 herewith is a clearer print of the tracheal cannula taken from the 1815 second edition of Curry. The obvious similarity to a Murphy style tube is striking. Curry states, "an instrument of this kind was originally proposed by M. Coleman, as an improvement upon a much narrower one invented by M. Kite." Also there is an illustration from the Annual Report of the Royal Humane Society (1806) showing the tracheal tube (fig. 11 in Mushin and Rendell-Baker).

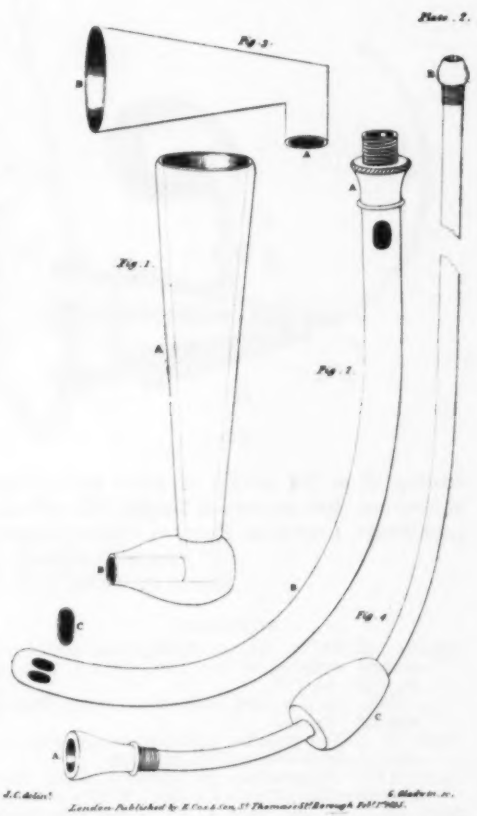


FIG. 1

At the Second World Congress in Toronto, the Scandinavian Society of Anaesthesiologists generously presented delegates with a reprint copy of Herholdt and Rafn (1796). The enclosed print (fig. 2) "showing Gorcy's Double Bellows" is taken from the reprint of Herholdt and Rafn. "h" is a flexible tube and instructions read: "he takes the catheter in his right hand, passes it along the left forefinger across the glottis and turns it carefully down into the windpipe".

I hope Dr. White and you, sir, will excuse the tardiness of this commentary. Both before and after the Toronto Congress, Boston, U.S.A., was blessed with many visiting savants from the United Kingdom and Commonwealth. We have been slowly recovering from the stimulation of the conversation and catching up on our journal

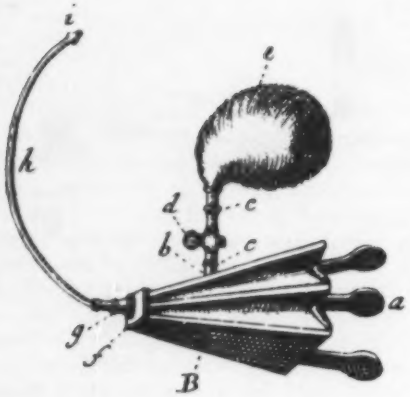


FIG. 2

reading. If in the travails of travel any of our visitors lost their pictures of Bunker Hill or Concord Bridge, I would be happy to replace them.

JOHN B. STETSON
Boston 15, Mass., U.S.A.

REFERENCES

Davison, M. H. A. (1951). Endotracheal and other modern methods in the 18th century. *Brit. J. Anaesth.*, **23**, 238.
—— (1960). The first endotracheal intubation. *Brit. J. Anaesth.*, **32**, 341.
Curry, J. (1792). *Popular observations on apparent death from drowning.* Northampton.
—— (1815). *Observations on apparent death from drowning* (2nd edition). London: E. Cox and Son.
Herholdt, J. D., and Rafn, C. G. (1796). *Life saving measures for drowning persons, etc.* Copenhagen: H. Tikiøb. Reprinted in English, Henning Poulson translator.
Mushin, W. W., and Rendell-Baker, L. (1953). *The principles of thoracic anaesthesia past and present*, p. 172. Oxford: Blackwell.

MAINTENANCE OF PIPED OXYGEN SUPPLIES

Sir,—Cylinder manifolds feeding oxygen pipelines in hospitals are all fitted with connectors adapted to be coupled to cylinder valves having an outlet in accordance with British Standard 341, which is $\frac{1}{4}$" righthand female thread. This type of valve is fitted to oxygen cylinders of 48 cu. ft. capacity and upwards and also to cylinders in this range which are used for compressed air, nitrogen, helium, helium/oxygen mixtures and oxygen/carbon dioxide mixtures. It is thus possible, for example, for a compressed air cylinder to be inadvertently connected to an oxygen pipeline. Personnel responsible for the maintenance of piped oxygen supplies should be reminded of this fact, and of the recommended code of practice with regard to the storage and handling of cylinders and the system of cylinder identification laid down in British Standard 1319:1955. Cylinders are painted in the characteristic colour according to the colour code shown in this B.S.I. standard and of course, also bear a printed label to identify the contents.

H. J. V. MORTON
Honorary Secretary,
Association of Anaesthetists of Great Britain and Ireland

A SPILL VALVE

Sir,—I was very interested in the spill valve described by Maxwell and Grant (*Brit. J. Anaesth.*, 1960, **32**, 616) and should like to point out that the inflating valve described by myself in 1958 is exactly the same in principle as that described by Maxwell and Grant, and can be used as they suggest. It can be obtained from Messrs. Charles King.

J. B. SEARLE
Folkestone

Sir,—With reference to the inflating valve described by Maxwell and Grant (*Brit. J. Anaesth.*, 1960, **32**, 316), an almost identical valve was described by Searle in 1958.

Although it was designed for use in the Magill circuit, I have found it very satisfactory when used in the semiclosed absorption set-up.

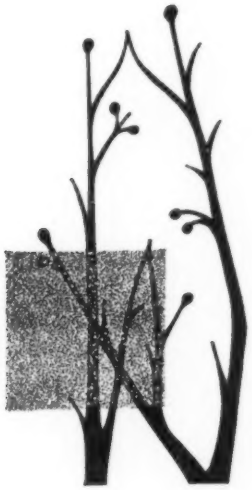
The valve may be obtained from the British Oxygen Company.

F. G. ETHERIDGE
Chertsey, Surrey

REFERENCE

Searle, J. B. (1958). Inflating valve. *Anaesthesia*, **13**, 345.

Printed in Great Britain by John Sherratt & Son, Park Road, Altrincham



duncaine*

The new name for

Lignocaine and your guarantee

that it is from

DUNCAN FLOCKHART OF EDINBURGH

The Doctors' House

*A registered trade mark, the property of

DUNCAN, FLOCKHART & CO LTD EDINBURGH 11

388

BRITISH JOURNAL OF ANAESTHESIA

VOLUME XXXIII, No. 4 *Published monthly* APRIL 1961

Annual subscription (post free): Inland £3 15s.; Overseas £4 4s.; U.S. and South Americas $12.00

CONTENTS

PAGE

EDITORIAL 173

SYMPOSIUM ON THE CENTRAL NERVOUS SYSTEM RELATED TO ANAESTHESIA

The reticular formation and ascending reticular system: anatomical considerations 174

By D. Bowsher, M.A., M.D., Department of Anatomy, University of Liverpool, England.

Brain mechanisms for wakefulness ... 183

By H. W. Magoun, Ph.D., Department of Anatomy, School of Medicine, University of California Medical Center, Los Angeles 24, California, U.S.A.

Some effects of anaesthesia on the brain 194

By Mary A. B. Brazier, D.Sc., Brain Research Institute, University of California, Los Angeles, and Center for Communication Sciences, Massachusetts Institute of Technology, Cambridge, U.S.A.

PAGE

Electroencephalography 205

By John Clutton-Brock, M.A., F.F.A.R.C.S., Department of Anaesthetics, Royal Infirmary, Bristol, England.

The importance of the central nervous effects of anaesthetic agents 214

By John Clutton-Brock, M.A., F.F.A.R.C.S., Department of Anaesthetics, Royal Infirmary, Bristol, England.

HISTORICAL

The evolution of premedication (II) ... 219

By W. M. Shearer, M.D., B.Sc., F.F.A.R.C.S., Department of Anaesthetics, The Royal Infirmary, Dundee, Scotland.

CORRESPONDENCE 226

JOHN SHERRATT & SON *Publishers* **PARK ROAD ALTRINCHAM ENGLAND**